10/523014

```
     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
L12          1090 S MAPKAP (W)KINASE##
L13          2622 S "MK2"
L14             0 S HEP25/27 (W)KINASE?
L15             0 S HEP25(W)27 (W)KINASE?
L16             0 S HEP25### (W)KINASE?
L17          3551 S L12 OR L13
L18         12206 S "SHC" OR "SRC (W)HOMOLOGY?"
L19            11 S L17 AND L18
L20             8 DUP REM L19 (3 DUPLICATES REMOVED)
L21         36782 S "SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"
L22             5 S L12 AND L21
L23             5 DUP REM L22 (0 DUPLICATES REMOVED)
L24             1 S L13 AND L21
L25             5 S L13 AND L18
L26           492 S MAP (W)KINASE-ACTIVATED(W) PROTEIN?
L27             3 S L21 AND L26
                  E YANNONI Y/AU
L28            48 S E3-E6
                  E LIN L L/AU
L29           521 S E3
L30           565 S L28 OR L29
L31             5 S L18 AND L30
L32             2 DUP REM L31 (3 DUPLICATES REMOVED)
L33          1465 S L21 AND YEAST?
L34             0 S L13 AND L33
L35             0 S L17 AND L33
L36          5973 S L18 AND (INTERACT OR BIND? OR ATTACH?)
L37           167 S L33 AND L36
L38            49 DUP REM L37 (118 DUPLICATES REMOVED)

=>
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PASSWORD:
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FILE 'MEDLINE' ENTERED AT 14:17:00 ON 27 JUL 2007
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	183.81	184.02

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-35.10	-35.10

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	183.81	184.02

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-35.10	-35.10

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FILE 'LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
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=> s mapkap (w)kinase##
L12         1090 MAPKAP (W) KINASE##

=> s "MK2"
L13         2622 "MK2"

=> s hep25/27 (w)kinase?
'27' IS NOT A VALID FIELD CODE
'27' IS NOT A VALID FIELD CODE
'27' IS NOT A VALID FIELD CODE
'27' IS NOT A VALID FIELD CODE
'27' IS NOT A VALID FIELD CODE
'27' IS NOT A VALID FIELD CODE
'27' IS NOT A VALID FIELD CODE
'27' IS NOT A VALID FIELD CODE
L14            0 HEP25/27 (W) KINASE?

=> s hep25(w)27 (w)kinase?
L15            0 HEP25(W) 27 (W) KINASE?

=> s hep25### (w)kinase?
L16            0 HEP25### (W) KINASE?

=> d his

     (FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007
L1         14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2          1588 S COLLAGEN AND L1
L3           202 S MINERAL AND L2
L4            67 S COMPOSIT? AND L3
L5            56 DUP REM L4 (11 DUPLICATES REMOVED)
L6             7 S (PORE OR DENSITY OR CM2) AND L5
                 E LI S T/AU
L7           701 S E3
                 E YUEN D/AU
L8            67 S E3
                 E CHEN H C/AU
L9          4244 S E3
L10         5010 S L7 OR L8 OR L9
L11            0 S L3 AND L10

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
L12         1090 S MAPKAP (W)KINASE##
L13         2622 S "MK2"
L14            0 S HEP25/27 (W)KINASE?
L15            0 S HEP25(W)27 (W)KINASE?
L16            0 S HEP25### (W)KINASE?
```

```
=> s l12 or l13
L17        3551 L12 OR L13

=> s "shc" or "src (w)homology?"
L18       12206 "SHC" OR "SRC (W)HOMOLOGY?"

=> s l17 and l18
L19          11 L17 AND L18

=> dup rem l19
PROCESSING COMPLETED FOR L19
L20            8 DUP REM L19 (3 DUPLICATES REMOVED)

=> d 1-8 ibib ab

L20   ANSWER 1 OF 8  BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
      DUPLICATE 1
ACCESSION NUMBER: 2004-09118  BIOTECHDS
TITLE:            New isolated, purified or recombinant protein complex
                  comprising an MK2 polypeptide, and an MK2
                  interacting protein chosen from STS, HPH2 and Shc
                  for treating or preventing e.g. Crohn's disease, or
                  rheumatoid arthritis;
                     involving vector-mediated gene transfer and expression in
                     host cell for use in gene therapy
AUTHOR:           LIN L; YANNONI Y M
PATENT ASSIGNEE:  WYETH
PATENT INFO:      WO 2004012660 12 Feb 2004
APPLICATION INFO: WO 2003-US23981 1 Aug 2003
PRIORITY INFO:    US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002
DOCUMENT TYPE:    Patent
LANGUAGE:         English
OTHER SOURCE:     WPI: 2004-156998 [15]
AB    DERWENT ABSTRACT:
      NOVELTY - An isolated, purified or recombinant protein complex comprising
      a mitogen-activated protein kinase-activated protein kinase 2 (
      MK2) polypeptide, and an MK2 interacting protein chosen
      from STS, HPH2 and Shc, is new.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the
      following: (1) a host cell comprising a first and a second nucleic acid,
      where the first nucleic acid encodes a recombinant MK2
      polypeptide and the second nucleic acid encoding MK2
      interacting protein; (2) an assay for determining whether the test
      compound inhibits or promotes formation of a protein complex; (3) a
      method for determining whether a test compound affects MK2
      activity; (4) an screening assay to identify compounds that inhibit or
      promote formation of the protein complex; (5) an antibody that binds one
      or more proteins in the complex; (6) a method for modulating formation of
      a protein complex in a cell comprising at least a first and a second
      protein; (7) a method for producing a complex; (8) a drug screening
      method for identifying anti-inflammatory drugs; (9) a method of
      modulating inflammation in a tissue; (10) a method of treating or
      preventing inflammation in a tissue; (11) a method of treating a patient
      suffering from at least one inflammatory condition; (12) a method of
      expressing a nucleic acid in a cell to inhibit inflammation; (13) a
      method of detecting at least one of the absence, presence and amount of
      MK2 in a sample; (14) a kit that enables qualitative detection of
      MK2 comprising a compound that interacts with at least one of
      MK2 or an MK2 complex, where the compound is chosen
      from an antibody, a chemical agent, a small molecule, a protein and a
      peptide; and at least one other kit component chosen from: at least one
      of buffer and solution; and at least one structural component; and (15) a
      pharmaceutical composition comprising at least one protein that binds
      MK2, and at least one carrier.
```

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The fusion protein comprises a domain chosen from affinity tags, radionucleotides, enzymes, and fluorophores. The domain is selected from polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region. Preferred Method: Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent

that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction, asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

L20 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:533778 HCAPLUS
DOCUMENT NUMBER:	141:65087
TITLE:	Gene expression-based method for distinguishing metastatic from non-metastatic forms of a tumor, and use in designing therapeutic drugs
INVENTOR(S):	Stephan, Dietrich A.; MacDonald, Tobey J.; Brown, Kevin M.
PATENT ASSIGNEE(S):	USA
SOURCE:	U.S. Pat. Appl. Publ., 17 pp. CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004126755	A1	20040701	US 2001-940454	20010829
PRIORITY APPLN. INFO.:			US 2001-940454	20010829

AB Gene expression profiling of tumors, clin. designated as either metastatic (M+) or non-metastatic (M0), identifies genes whose expression differed significantly between classes. A class-prediction algorithm based on these medulloblastoma genes assigned the sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with a 100% accuracy. Class prediction also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably upregulated in the M+ tumors were platelet derived growth factor receptor alpha (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway. Immunohistochem. validation on an independent set of tumors showed significant overexpression of PDGFRA in M+ tumors as compared to M0 tumors. In in vitro assays, PDGFA enhanced medulloblastoma migration and increased downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK), and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA or U0126, a highly specific chemical inhibitor of MAP2K1 and MAP2K2 known as U0126, blocked MAP2K1, MAP2K2, and MAPK1/3 phosphorylation, inhibited migration, and prevented PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins, among others overexpressed M+ genes identified herein, represent novel therapeutic targets in medulloblastomas and other M+/MO tumors. The inventive method of prediction and targeted therapy is applicable to any tumor that exists in both M+ and MO forms, such as the neurotumors glioma, neuroblastoma and ependymoma, as well as lung and breast cancers.

L20 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER:	2004196650 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 15094067
TITLE:	P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.
AUTHOR:	Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE:	Department of Inflammation, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140-2311, USA.. yvonne.yannoni@abbott.com
SOURCE:	FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY:	Netherlands
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200406
ENTRY DATE:	Entered STN: 20 Apr 2004 Last Updated on STN: 4 Jun 2004 Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

L20 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:942767 HCAPLUS
DOCUMENT NUMBER: 140:40262
TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XB38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 2002-374547P	P	20020423
US 2002-420784P	P	20021024
US 2002-421043P	P	20021025
US 2002-424680P	P	20021108
WO 2002-US38221	A	20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L20 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:409169 HCAPLUS
DOCUMENT NUMBER: 138:380506
TITLE: Genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses
INVENTOR(S): Brissette, William H.; Neote, Kuldeep S.; Zagouras, Panayiotis; Zenke, Martin; Lemke, Britt; Hacker, Christine
PATENT ASSIGNEE(S): Pfizer Products Inc., USA; Max-Delbrueck-Centrum Fuer Molekulare Medizin
SOURCE: PCT Int. Appl., 285 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003038130	A2	20030508	WO 2002-XA34888	20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003038130	A2	20030508	WO 2002-US34888	20021031
WO 2003038130	A3	20040212		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

US 2001-335048P	P	20011031
US 2001-335183P	P	20011102
WO 2002-US34888	A	20021031

AB The present invention provides mol. targets that regulate erythropoiesis. Groups of genes or their encoded gene products comprise panels of the invention and may be used in therapeutic intervention, therapeutic agent screening, and in diagnostic methods for diseases and/or disorders of erythropoiesis. The panels were discovered using gene expression profiling of erythroid progenitors with Affymetrix HU6800 and HG-U95Av2 chips. Cells from an in vitro growth and differentiation system of SCF-Epo dependent human erythroid progenitors, E-cadherin+/CD36+ progenitors, cord blood, or CD34+ peripheral blood stem cells were analyzed. The HU6800 chip contains probes from 13,000 genes with a potential role in cell growth, proliferation, and differentiation and the HG-U95Av2 chip contains 12,000 full-length, functionally-characterized genes. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L20 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:851837 HCAPLUS
DOCUMENT NUMBER: 141:104117
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease. [Erratum to document cited in CA136:051990]
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2003), 35(3), 287

CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The annotation for the Affymetrix G110 probe set 1770 that was used was incorrect. Although the annotation specifies that the transcript for PDGFR-α is being ascertained, the true specificity of the probe set is for the PDGFR-β isoform. The ligand for both receptor isoforms is identical. The functional validation of the PDGFR signaling pathway, described in our article, used specific neutralizing antibodies against PDGFR-α as well as downstream small mol. inhibitors, and it implicates this entire cascade. The PDGFR-β isoform may be more relevant in the metastatic process, but this does not discount the proven biol. role of PDGFR-α and downstream effectors in metastatic medulloblastoma.

L20 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:615889 HCAPLUS
DOCUMENT NUMBER: 137:180730
TITLE: Human cDNA/DNA molecules and proteins encoded by them with enhanced expression in apoptosis-resistant cell clones, and use thereof in diagnosis, therapeutics and drug screening
INVENTOR(S): Ullrich, Axel; Abraham, Reimar
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002063037	A2	20020815	WO 2002-EP1073	20020201
WO 2002063037	A3	20031002		
WO 2002063037	A9	20040219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2434881	A1	20020815	CA 2002-2434881	20020201
AU 2002249170	A1	20020819	AU 2002-249170	20020201
AU 2002249170	B2	20070208		
EP 1364066	A2	20031126	EP 2002-718083	20020201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004517638	T	20040617	JP 2002-562773	20020201
US 2004110177	A1	20040610	US 2003-470845	20030731
AU 2007201963	A1	20070524	AU 2007-201963	20070502

PRIORITY APPLN. INFO.:			
US 2001-265631P	P	20010202	
AU 2002-249170	A3	20020201	
WO 2002-EP1073	W	20020201	

AB The present invention relates to a method for identifying nucleic acid mols. functionally associated with a desired phenotype, such as cancer cell properties, including anti-apoptosis. The method, which allows for generation of expression profiles of genes associated with said desired

phenotype, involves a mutagenesis and/or genome rearrangement step, followed by selection of cell clones displaying the desired phenotype. The invention also relates that the method involves the use of the following techniques: fluorescence-activated cell sorting (FACS); nucleic acid microarray (cDNA, genomic or oligonucleotide); protein array; two-dimensional gel electrophoresis; and/or mass spectrometry. The invention further relates that the disclosed method was used to identify genes, which are differentially expressed in apoptosis-sensitive and apoptosis-resistant cells. Specifically, the invention relates that apoptosis was induced in human cervix carcinoma cell line HeLa S3 by Fas activation. After the selection procedure, only a low number of living cells were present, which had a higher resistance against apoptosis than the parental cell line. MRNA was isolated from these surviving clones, and from the parental cell line, and transcribed into cDNA. CDNA microarray technol. was used to identify about 150-200 genes (cDNA/DNA mols.) that exhibited enhanced expression in apoptosis-resistant clones. The GenBank accession nos. of some of these cDNA/DNA mols. are provided, along with the products encoded by said mols. Still further, the invention relates that most of the apoptosis-associated genes encode protein phosphatases, and kinases. Finally, the invention relates that said nucleic acid mols., and proteins encoded by mols., can be used as targets in diagnosis, therapeutics and drug screening, particularly for disorders associated with dysfunction of apoptotic processes, such as tumors.

L20 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:756373 HCAPLUS
DOCUMENT NUMBER: 136:51990
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2001), 29(2), 143-152
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Little is known about the genetic regulation of medulloblastoma dissemination, but metastatic medulloblastoma is highly associated with poor outcome. We obtained expression profiles of 23 primary medulloblastomas clin. designated as either metastatic (M+) or non-metastatic (M0) and identified 85 genes whose expression differed significantly between classes. Using a class prediction algorithm based on these genes and a leave-one-out approach, we assigned sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with 100% accuracy. We also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably, platelet-derived growth factor receptor α (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway are upregulated in M+ tumors. Immunohistochem. validation on an independent set of tumors shows significant overexpression of PDGFRA in M+ tumors compared to M0 tumors. Using in vitro assays, we show that platelet-derived growth factor α (PDGFA) enhances medulloblastoma migration and increases downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK) and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA blocks MAP2K1, MAP2K2 and MAPK1/3 phosphorylation, whereas U0126, a highly specific inhibitor of MAP2K1 and MAP2K2, also blocks MAPK1/3. Both inhibit migration and prevent PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for PDGFRA and the RAS/MAPK

signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins should therefore be considered for investigation as possible novel therapeutic strategies against medulloblastoma.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007

```
L1        14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2         1588 S COLLAGEN AND L1
L3          202 S MINERAL AND L2
L4           67 S COMPOSIT? AND L3
L5           56 DUP REM L4 (11 DUPLICATES REMOVED)
L6            7 S (PORE OR DENSITY OR CM2) AND L5
                E LI S T/AU
L7          701 S E3
                E YUEN D/AU
L8           67 S E3
                E CHEN H C/AU
L9         4244 S E3
L10        5010 S L7 OR L8 OR L9
L11           0 S L3 AND L10
```

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007

```
L12        1090 S MAPKAP (W)KINASE##
L13        2622 S "MK2"
L14           0 S HEP25/27 (W)KINASE?
L15           0 S HEP25(W)27 (W)KINASE?
L16           0 S HEP25### (W)KINASE?
L17        3551 S L12 OR L13
L18       12206 S "SHC" OR "SRC (W)HOMOLOGY?"
L19          11 S L17 AND L18
L20           8 DUP REM L19 (3 DUPLICATES REMOVED)
```

=> d 1-8 ibib ab kwic

L20 ANSWER 1 OF 8 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
DUPLICATE 1

ACCESSION NUMBER: 2004-09118 BIOTECHDS

TITLE: New isolated, purified or recombinant protein complex comprising an MK2 polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc for treating or preventing e.g. Crohn's disease, or rheumatoid arthritis;
involving vector-mediated gene transfer and expression in host cell for use in gene therapy

AUTHOR: LIN L; YANNONI Y M

PATENT ASSIGNEE: WYETH

PATENT INFO: WO 2004012660 12 Feb 2004

APPLICATION INFO: WO 2003-US23981 1 Aug 2003

PRIORITY INFO: US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2004-156998 [15]

AB DERWENT ABSTRACT:

NOVELTY - An isolated, purified or recombinant protein complex comprising a mitogen-activated protein kinase-activated protein kinase 2 (MK2) polypeptide, and an MK2 interacting protein chosen

from STS, HPH2 and Shc, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a host cell comprising a first and a second nucleic acid, where the first nucleic acid encodes a recombinant MK2 polypeptide and the second nucleic acid encoding MK2 interacting protein; (2) an assay for determining whether the test compound inhibits or promotes formation of a protein complex; (3) a method for determining whether a test compound affects MK2 activity; (4) an screening assay to identify compounds that inhibit or promote formation of the protein complex; (5) an antibody that binds one or more proteins in the complex; (6) a method for modulating formation of a protein complex in a cell comprising at least a first and a second protein; (7) a method for producing a complex; (8) a drug screening method for identifying anti-inflammatory drugs; (9) a method of modulating inflammation in a tissue; (10) a method of treating or preventing inflammation in a tissue; (11) a method of treating a patient suffering from at least one inflammatory condition; (12) a method of expressing a nucleic acid in a cell to inhibit inflammation; (13) a method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and at least one other kit component chosen from: at least one of buffer and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The fusion protein comprises a domain chosen from affinity tags, radionucleotides, enzymes, and fluorophores. The domain is selected from polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region. Preferred Method: Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins,

where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction, asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

TI New isolated, purified or recombinant protein complex comprising an MK2 polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc for treating or preventing e.g. Crohn's disease, or rheumatoid arthritis;
involving vector-mediated gene transfer and expression in host cell for. . .

AB DERWENT ABSTRACT:
NOVELTY - An isolated, purified or recombinant protein complex comprising a mitogen-activated protein kinase-activated protein kinase 2 (MK2) polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a host cell comprising a first and a second nucleic acid, where the first nucleic acid encodes a recombinant MK2 polypeptide and the second nucleic acid encoding MK2 interacting protein; (2) an assay for determining whether the test compound inhibits or promotes formation of a protein complex; (3) a method for determining whether a test compound affects MK2 activity; (4) an screening assay to identify compounds that inhibit or promote formation of the protein complex; (5) an antibody. . . a cell to inhibit inflammation; (13) a method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide;. . . and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The. . . Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the. . . in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where

the two proteins interact in the two hybrid assay system; measuring a level of interaction between the. . . proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition,. . . a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide;. . . the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an. . .

CT RECOMBINANT MK2 PROTEIN PREP., ISOL., VECTOR-MEDIATED GENE TRANSFER, EXPRESSION IN HOST CELL, APPL. INFLAMMATORY BOWEL DISEASE,

ULCERATIVE COLITIS, RHEUMATOID ARTHRITIS, ACUTE RESPIRATORY. . .

L20 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:533778 HCAPLUS
DOCUMENT NUMBER: 141:65087
TITLE: Gene expression-based method for distinguishing metastatic from non-metastatic forms of a tumor, and use in designing therapeutic drugs
INVENTOR(S): Stephan, Dietrich A.; MacDonald, Tobey J.; Brown, Kevin M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004126755	A1	20040701	US 2001-940454	20010829
PRIORITY APPLN. INFO.:			US 2001-940454	20010829

AB Gene expression profiling of tumors, clin. designated as either metastatic (M+) or non-metastatic (M0), identifies genes whose expression differed significantly between classes. A class-prediction algorithm based on these medulloblastoma genes assigned the sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with a 100% accuracy. Class prediction also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably upregulated in the M+ tumors were platelet derived growth factor receptor alpha (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway. Immunohistochem. validation on an independent set of tumors showed significant overexpression of PDGFRA in M+ tumors as compared to M0 tumors. In in vitro assays, PDGFA enhanced medulloblastoma migration and increased downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK), and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA or U0126, a highly specific chemical inhibitor of MAP2K1 and MAP2K2 known as U0126, blocked MAP2K1, MAP2K2, and MAPK1/3 phosphorylation, inhibited migration, and prevented PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins, among others overexpressed M+ genes identified herein, represent novel therapeutic targets in medulloblastomas and other M+/MO tumors. The inventive method of prediction and targeted therapy is applicable to any tumor that exists in both M+ and MO forms, such as the neurotumors glioma, neuroblastoma and ependymoma, as well as lung and breast cancers.

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SHC; gene expression-based method for distinguishing metastatic from non-metastatic tumors, and use in designing therapeutic drugs)

IT 9012-90-2, DNA polymerase 9013-66-5, Glutathione peroxidase 9025-26-7, Cathepsin D 9027-03-6, Ubiquinol cytochrome c reductase 9032-68-2, Cathepsin C 9035-51-2, Cytochrome P 450, biological studies 9035-54-5, Placental lactogen 37353-41-6, Cysteine protease 50812-37-8, Glutathione S-transferase 74812-49-0 80449-02-1, Tyrosine kinase 83268-44-4 86102-31-0, TIMP 115926-52-8, PI 3-kinase 127464-60-2, Vascular endothelial growth factor 141436-78-4, Protein kinase C 142008-29-5, CAMP-dependentprotein kinase 142243-02-5, Mitogen-activated protein kinase 142805-58-1, MEK1 kinase 148348-15-6, Fibroblast growth factor 7 148640-14-6, Rac protein kinase 149885-84-7, Dual-specificity protein phosphatase 150316-14-6, MEK2 kinase 151769-16-3,

TNF-α-converting enzyme 161052-08-0, Tie receptor tyrosine kinase 289898-51-7, Jnk1 kinase 377752-08-4, Ribosomal protein S6 kinase 2 397251-44-4, MAPKAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (gene expression-based method for distinguishing metastatic from non-metastatic tumors, and use in designing therapeutic drugs)

L20 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004196650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15094067
TITLE: P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.
AUTHOR: Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE: Department of Inflammation, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140-2311, USA. yvonne.yannoni@abbott.com
SOURCE: FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20 Apr 2004
Last Updated on STN: 4 Jun 2004
Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

TI P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

L20 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:942767 HCAPLUS
DOCUMENT NUMBER: 140:40262
TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XB38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
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WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:	US 2002-374547P	P	20020423
	US 2002-420784P	P	20021024
	US 2002-421043P	P	20021025
	US 2002-424680P	P	20021108
	WO 2002-US38221	A	20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT 444967-60-6 444967-64-0 444967-94-6 444968-02-9 444968-33-6 445046-93-5 445046-97-9, Keratin 18 (human gene KRT18) 445047-05-2 445047-24-5 445047-26-7 445047-27-8 459481-13-1 459483-00-2, Protein (human 461-amino acid) 459483-69-3, GenBank AAA35587 459485-04-2 459488-59-6 459488-70-1 459490-09-6 459492-63-8, GenBank CAA80258 459499-49-1 459501-90-7, GenBank BAA09534 459503-60-7 459503-76-5 459504-00-8, GenBank AAC51926 459504-82-6, GenBank AAC33794 459504-86-0 459506-17-3, GenBank BAA76810 459509-52-5 459511-39-8 459512-24-4, GenBank BAA00472 459512-52-8, Protein (human 364-amino acid) 459512-91-5, Protein (human 346-amino acid) 459513-03-2 459513-39-4, Protein (human 145-amino acid) 459513-52-1, GenBank CAA26203 459513-68-9, Protein (human gene LYN) 459514-36-4, GenBank AAA59482 459515-65-2, GenBank AAA51554 459516-86-0, GenBank CAA26306 459517-04-5, Protein (human 437-amino acid) 459518-52-6 459518-75-3, GenBank AAA60964 459519-13-2 459519-50-7 459520-26-4, Laminin (human gene LAMB2 B2 chain) 459520-72-0 459521-00-7, Protein 14.3.3 (human Jurkat cell) 459521-43-8 459522-09-9 459522-11-3, GenBank AAA03476 459522-98-6, HLA-DMB (human) 459523-02-5 459523-19-4 459523-82-1, GenBank AAC51320 459524-46-0, Iron regulatory factor (human) 459524-52-8, 14-3-3 Protein (human clone hBM5) 459525-21-4 459525-39-4, GenBank CAA46050 459525-94-1 459526-16-0 459526-47-7, GenBank CAA47471 459526-75-1, GenBank AAB92356 459527-67-4, GenBank AAA60119

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RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(amino acid sequence; genes expressed in atherosclerotic tissue and
their use in diagnosis and pharmacogenetics)

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RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics)

L20 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:409169 HCAPLUS
DOCUMENT NUMBER: 138:380506
TITLE: Genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses
INVENTOR(S): Brissette, William H.; Neote, Kuldeep S.; Zagouras, Panayiotis; Zenke, Martin; Lemke, Britt; Hacker, Christine
PATENT ASSIGNEE(S): Pfizer Products Inc., USA; Max-Delbrueck-Centrum Fuer Molekulare Medizin
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003038130	A2	20030508	WO 2002-XA34888	20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,				

UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
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WO 2003038130 A2 20030508 WO 2002-US34888 20021031
WO 2003038130 A3 20040212
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PRIORITY APPLN. INFO.: US 2001-335048P P 20011031
US 2001-335183P P 20011102
WO 2002-US34888 A 20021031

AB The present invention provides mol. targets that regulate erythropoiesis. Groups of genes or their encoded gene products comprise panels of the invention and may be used in therapeutic intervention, therapeutic agent screening, and in diagnostic methods for diseases and/or disorders of erythropoiesis. The panels were discovered using gene expression profiling of erythroid progenitors with Affymetrix HU6800 and HG-U95Av2 chips. Cells from an in vitro growth and differentiation system of SCF-Epo dependent human erythroid progenitors, E-cadherin+/CD36+ progenitors, cord blood, or CD34+ peripheral blood stem cells were analyzed. The HU6800 chip contains probes from 13,000 genes with a potential role in cell growth, proliferation, and differentiation and the HG-U95Av2 chip contains 12,000 full-length, functionally-characterized genes. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT 459518-11-7, GenBank CAA61579 459518-51-5 459518-52-6 459518-87-7, G-Protein β-3 chain (human gene GNB3) 459519-04-1 459519-11-0, Protein (human 586-amino acid) 459519-31-4 459519-47-2, GenBank CAA38401 459519-50-7 459519-86-9 459520-02-6 459520-15-1 459520-60-6, GenBank AAA03652 459520-72-0 459520-85-5, Nuclear autoantigen (human gene Sp-100) 459521-00-7, Protein 14.3.3 (human Jurkat cell) 459521-60-9 459521-62-1, Arnt (human cell line HepG2 gene ARNT) 459521-86-9 459521-96-1, Protein (human clone G16 345-amino acid) 459522-07-7, GenBank AAA35860 459522-10-2, GenBank CAB56794 459522-11-3, GenBank AAA03476 459522-20-4 459522-79-3, GenBank CAB02541 459522-84-0 459522-94-2, GenBank CAA40016 459522-95-3, Moesin B (human cell HL 60) 459522-98-6, HLA-DMB (human) 459523-01-4 459523-02-5 459523-06-9, GenBank AAC78725 459523-18-3, GenBank AAA16105 459523-19-4 459523-43-4, Phosphate carrier protein (human) 459523-47-8, GenBank AAA59531 459523-58-1 459523-95-6 459524-17-5, Protein (human gene PGM1) 459524-29-9, GenBank AAA35641 459524-46-0, Iron regulatory factor (human) 459524-52-8, 14-3-3 Protein (human clone hBM5) 459525-65-6 459525-88-3, ATPase (human) 459525-94-1 459526-16-0 459526-33-1 459526-46-6, GenBank CAA49189 459526-75-1, GenBank AAB92356 459527-06-1, GenBank CAA47285 459527-66-3, GenBank CAA78475 459528-15-5 459528-29-1, Protein (human gene GPI-H) 459528-38-2, GenBank AAC50130 459528-44-0, GenBank AAA36729 459528-71-3, Protein (human gene AF-9) 459528-72-4, Protein (human gene AF-4) 459528-84-8 459529-02-3, GenBank AAB02036 459529-44-3 459530-14-4, Protein p78 (human gene p78) 459530-41-7 459530-42-8, GenBank CAA46519 459531-45-4 459531-84-1 459531-91-0 459532-05-9, GenBank AAA18945 459532-32-2, GenBank CAA59689 459532-38-8 459532-55-9, GenBank AAA36443 459532-58-2, GenBank AAA19251 459532-87-7, GenBank CAA54417 459533-17-6, GenBank CAA63295

459533-28-9 459533-74-5, GenBank AAB40977 459534-62-4, GenBank CAA73107 459534-79-3, GenBank AAA59187 459535-03-6, GenBank CAA56730 459535-11-6, Protein p84 (human clone N5-4) 459535-29-6 459535-48-9 459535-52-5 459535-64-9 459535-67-2, GenBank AAB88724 459536-19-7 459536-28-8, GenBank AAA81905 459536-29-9 459536-66-4, ALDH7 (human clone ALDH7) 459536-74-4, DAP-1 (human cell line HL-60 gene DAP-1) 459536-84-6, Cell surface glycoprotein (human) 459536-88-0 459536-90-4 459537-18-9, Protein HFcRn (human clone 11/3) 459537-57-6, GenBank CAA99732 459538-25-1 459538-37-5, GenBank AAA03192 459538-91-1, PRK2 (human) 459539-00-5, GenBank CAA63224 459539-55-0, Prostasin (human strain Caucasian) 459540-22-8, FXR1 (human) 459540-27-3 459540-33-1, GenBank CAA56489 459540-34-2, GenBank CAA56491 459541-39-0, GenBank AAA80581 459541-60-7 459541-83-4, GenBank AAB96827 459541-99-2, A-Glucosidase I (human) 459542-16-6, Protein (human clone 126 gene DR-nm-23) 459542-21-3 459542-26-8 459542-28-0, CDK8 protein kinase (human gene CDK8) 459542-52-0 459542-79-1, GenBank AAC50205 459543-02-3, GenBank AAA91458 459543-14-7, GenBank AAA86686 459543-17-0, GenBank CAA65633 459543-31-8, GenBank AAC50294 459543-60-3, GenBank AAB07513 459543-66-9, GenBank AAC50289 459543-68-1, GenBank AAB36088 459543-74-9, Dihydropyrimidine dehydrogenase (human) 459548-52-8, HPMSR6 (human gene hPMSR6) 459548-58-4, GenBank AAC50292 459548-78-8, GenBank CAA60384 459548-83-5, GenBank AAC50350 459549-42-9, GenBank CAA59449 459549-69-0 459549-73-6, Yeast sds-22 (human gene sds-22) 459549-85-0 459550-13-1, GenBank AAC50461 459550-26-6, GenBank AAC41949 459550-67-5, GenBank AAC16912 459550-74-4, P126 (Human gene ST5) 459550-78-8, Cystatin B (human gene cystatin B) 459551-48-5, Glycogenin (human) 459551-64-5, GenBank AAC50433 459551-65-6, Antisecretory factor-1 (human) 459552-32-0, GenBank CAA63418 459552-43-3, SMT3B protein (human gene SMT3B) 459552-61-5, A-1 (Human gene A) 459552-63-7, A-2 (Human gene A) 459552-64-8, B (Human gene B) 459552-66-0, Isopeptidase T (human gene ISOT) 459552-68-2, Isopeptidase T (human gene ISOT) 459552-77-3, CTCF (human cell line HL-60 gene CTCF) 459552-80-8 459552-93-3, GAP SH3 binding protein (human) 459552-96-6, GenBank AAB09758 459553-19-6, Protein Nmi (human gene Nmi) 459553-37-8, SNAP-23 (human) 459553-39-0, GenBank AAB06188 459553-40-3, GenBank AAC50512 459553-66-3, GenBank AAC12660 459553-74-3 459553-76-5, GenBank AAC50555 459553-97-0 459554-37-1, Protein (human gene PEA-15) 459554-94-0 459555-03-4, GenBank AAB17087 459555-04-5, GenBank AAC39657 459555-27-2, GenBank AAB08975 459555-32-9, Cofactor C (human) 459555-43-2 459555-92-1 459555-99-8, GenBank CAA63213 459556-00-4, Protein (human gene ITBA2) 459556-07-1 459556-11-7, GenBank CAA63069 459556-21-9, GenBank AAC05330 459556-43-5, YKL-39 precursor (human) 459556-46-8, GenBank AAB07119 459556-80-0, I-TRAF (human) 459556-82-2, GenBank AAC50641 459557-27-8 459562-85-7, GenBank AAC50695 459576-39-7 459576-40-0, SMT3C protein (human gene SMT3C) 459576-70-6, GenBank AAB36871 459577-04-9, GenBank AAB49751 459577-11-8, GenBank AAB18823 459577-23-2, Ste-20-like kinase (human) 459577-30-1 459577-55-0, Ubiquitin hydrolase (human gene DFFRX) 459577-66-3, FX (human) 459577-70-9, GenBank AAB07689 459577-71-0, GenBank AAC50731 459578-19-9, GenBank AAB05814 459578-44-0, GenBank AAB60432 459578-94-0 459578-98-4, GenBank AAB46370 459579-18-1, GenBank AAB36682 459579-29-4, GenBank CAA57478 459579-54-5 459579-93-2, Ataxin 2 (human gene SCA2) 459580-08-6, Protein CGR19 (human clone hCGR19) 459580-36-0, YMP (human gene YMP) 459580-37-1 459580-45-1, GenBank CAA68851 459580-57-5, GenBank AAA62269 459580-63-3, CC chemokine STCP-1 (human) 459580-66-6, GenBank AAC50898 459580-98-4 459581-12-5, Protein (human gene OLF3) 459581-20-5 459581-85-2, TIF1-beta zinc finger protein (human) 459581-86-3, GenBank AAB51517 459582-00-4, GenBank AAB42217 459582-04-8, GenBank CAA55356 459582-06-0, GenBank AAB41495 459582-07-1, Osteoclast stimulating factor (human) 459582-40-2 459582-44-6, Kinase Myt-1 (human gene Myt-1) 459582-46-8, GenBank CAA64670 459582-49-1 459582-52-6, GenBank AAC50995 459583-84-7,

GenBank AAC51127 459584-48-6, Bikunin (human) 459584-81-7, GenBank AAB49031 459584-97-5 459585-04-7 459585-15-0, GenBank AAC51173 459585-24-1, Aminopeptidase (human) 459585-28-5, GenBank AAB51514 459585-31-0, GenBank AAB48596 459585-32-1 459585-39-8, GenBank CAA69904 459585-49-0, GenBank CAA70761 459585-75-2, GenBank CAA67896 459585-84-3, P66-Shc (human gene SHC) 459585-90-1, C8 (Human gene C8) 459585-91-2, C9 (Human gene C9) 459585-92-3, B7 (Human gene B7) 459585-93-4, DRPLA (human gene HUMDRPLA1) 459585-95-6, C2f (Human gene C2f) 459585-96-7, GenBank AAC51640 459585-97-8, C3f (Human gene C3f) 459586-22-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses)
IT 480943-69-9 480943-73-5, Dynamitin (human) 480943-77-9 480943-82-6, Trans-Golgi p230 (human) 480943-92-8, UHX1 protein (human gene UHX1) 480943-99-5, Ikaros/LyF-1 (human gene hIk-1) 480944-04-5 480944-06-7, Diacylglycerol kinase zeta (human) 480944-09-0, Metaxin (human gene MTX) 480944-11-4 480944-41-0, Hs-CUL-1 (human gene Hs-cul-1) 480944-43-2, Hs-CUL-3 (human gene Hs-cul-3) 480944-46-5, BA46 (human) 480944-52-3, TSC-22 protein (human) 480944-71-6 480944-83-0, VHL binding protein-1 (human gene VBP-1) 480944-89-6 480944-94-3 480945-09-3 480945-16-2 480945-17-3, DNA polymerase gamma (human) 480945-22-0, STAM (human) 480945-59-3 480945-60-6 480946-15-4, NifU-like protein (human gene hNifU) 480946-16-5 480946-17-6, GenBank AAC50889 480946-18-7, FUSE binding protein 3 (human gene FBP3) 480946-20-1, Soluble protein Jagged (human) 480946-23-4, Acetolactate synthase (human) 480947-84-0 480947-92-0, Menin (human gene MEN1) 480947-93-1, Menin (human gene MEN1) 480947-94-2, HsPex7p (human gene HsPEX7) 480948-05-8, C2H2-150 (human) 480948-06-9, GenBank AAC51298 480948-23-0, CREB-binding protein (human clone cRT16) 480948-30-9, Phosphomannomutase (human gene PMM2) 480948-31-0 480950-79-6 480950-82-1, Zinc finger protein (human clone PRD51) 480952-54-3 480952-92-9 480953-02-4, P43 (human gene P43) 480953-78-4 480954-49-2, GenBank AAC64483 480958-41-6, Protein MRE11 (human) 480958-70-1, Alpha SNAP (human) 480959-26-0, Tryptase-I (human) 481118-85-8 481123-85-7, PP35 (human) 481123-88-0 481123-89-1 481123-95-9, No arches (human gene nar) 481125-18-2 481126-83-4, AP-3 complex delta subunit (human) 481126-84-5, AP-3 complex sigma3A subunit (human) 481128-21-6, MAPKAP kinase (human clone 3pK gene 3pK) 481128-47-6, DPH2L (human clone B2-3.1) 481128-88-5 481128-89-6, GenBank AAA66020 481128-90-9 481129-09-3 481132-23-4 481135-33-5, Cystic fibrosis antigen (human) 481135-38-0 481135-94-8 481135-96-0 481136-09-8 481136-21-4, Protein (human gene DP-2) 481137-32-0 481137-54-6 481137-57-9 481138-63-0 481138-95-8, Protein (human gene CD19) 481143-79-7 481145-07-7 481150-24-7 481150-30-5 481150-42-9 481150-53-2, Sulfite oxidase (human) 481150-87-2 481151-66-0 481151-93-3 481151-94-4 481152-07-2, HPAK65 (human gene hPAK65) 481152-10-7, Elongin A (human clone pSPORT 1) 481152-79-8 481152-80-1 481153-08-6 481153-10-0 481157-48-6 481158-22-9 481158-89-8, Trophinin (human clone HTH55) 481158-91-2, DNA binding protein (human gene HPF2) 481167-58-2 481168-59-6 481168-67-6, 100 KDa coactivator (human) 481168-68-7, L-iditol-2 dehydrogenase (human) 481168-69-8, L-iditol-2 dehydrogenase (human) 481169-13-5, Lamin B2 (human gene LAMB2) 481169-39-5 481169-76-0, GenBank AAA82559 481169-84-0 481170-45-0 481170-75-6, P57KIP2 (human gene KIP2) 481170-93-8, B4-2 protein (human clone B4-2) 481170-95-0 481171-13-5 481171-27-1 481171-28-2, Csa-19 (human) 481171-35-1 481171-86-2 481171-88-4 481171-93-1 481172-22-9 481172-35-4, Protein (human 83-amino acid) 481172-57-0, Glycophorin A (human gene GYPA) 481172-64-9 481172-65-0 481172-87-6 481172-88-7 481172-93-4 481172-94-5 481173-21-1, UV-damaged DNA binding factor (human) 481173-32-4 481173-36-8 481173-38-0 481173-44-8 481173-48-2, Protein (human gene DSS1) 481173-55-1, HnRNP H (human cell line MRC-5 V2) 481173-60-8 481173-61-9, UbcH5B (human

gene UBCH5B) 481173-62-0, UbcH5C (human gene UBCH5C) 481173-69-7, Tis11d (human) 481173-72-2 481173-78-8 481173-96-0 481173-98-2 481174-26-9 481174-31-6, PL6 protein (human clone PL6 gene PL6) 481174-49-6, Protein (human gene LYL1) 481174-55-4 481174-61-2 481174-62-3 481174-68-9 481174-76-9, SRp40-1 (human gene SRp40) 481174-77-0 481175-06-8 481175-07-9, Transcription factor (human gene MEF2) 481175-18-2 481175-34-2, Protein (human gene FRG1) 481175-37-5 481175-41-1 481175-66-0, Protein (human 387-amino acid) 481175-93-3 481176-07-2, CREB-RP (human gene creb-rp) 481176-08-3, HPMSR2 (human gene hPMSR2) 481176-09-4, HPMSR3 (human gene hPMSR3) 481176-11-8, Protein (human gene TCTA) 481176-26-5, ZNF157 (human gene ZNF157) 481176-30-1, Adenosine kinase (human) 481176-61-8 481176-63-0, Frataxin (human gene FRDA) 481177-04-2 481177-06-4, Calbindin 27 (human) 481177-17-7 481177-18-8 481178-43-2, Protein (human clone LUCA15 gene LUCA15) 481178-48-7, Prolylcarboxypeptidase (human) 481178-67-0 481178-97-6, E2F-5 (human) 481179-50-4, Protein (human gene HEXA) 481179-57-1 481179-64-0, Dihydrolipoamide dehydrogenase (human) 481179-98-0, Deoxyhypusine synthase (human) 481179-99-1 481180-02-3 481180-14-7, Protein phosphatase-1 inhibitor (human) 481180-44-3 481180-45-4 481180-56-7, Protein (human 329-amino acid) 481180-57-8, Protein (human 232-amino acid) 481180-61-4 481181-27-5 481181-45-7 481181-57-1 481182-47-2, Protein G0S2 (human gene G0S2) 481182-64-3 481182-72-3 481183-02-2 481183-06-6 481183-14-6 481183-32-8 481183-49-7, CALM (human gene CALM) 481183-51-1 481183-72-6, Glutaryl-CoA dehydrogenase (human) 481184-01-4, P2X5a (human) 481184-05-8 481184-11-6 481184-22-9 481186-99-6 481188-52-7, 2,4-Dienoyl-CoA reductase (human) 481188-53-8 481195-74-8 481195-80-6, MAP kinase kinase MEK5b (human) 481195-82-8 481196-01-4, Adducin gamma subunit (human) 481196-11-6 481196-30-9 481196-49-0 481196-70-7 481196-81-0, Protein (human 177-amino acid) 481196-98-9 481197-01-7 481197-28-8, HMFG (human gene HMFG) 481198-32-7 481198-65-6, Protein (human gene prohibitin) 481198-91-8 481200-09-3, HZF-16.2 (human gene HZF-16) 481200-10-6, HZF-16.1 (human gene HZF-16) 481200-42-4 481200-95-7, TLS (human gene TLS) 481201-13-2, FBRNP (human gene D10S102) 481201-33-6 481201-34-7 481201-67-6 481201-91-6 481202-22-6 481202-29-3 481202-48-6 481202-63-5, APK1 antigen (human gene APK1 antigen) 481202-99-7 481203-70-7 481203-83-2, IK factor (human gene IK) 481203-85-4, E2F-4 (human gene E2F-4) 481204-50-6, AML1 (human gene AML1)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses)

L20 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:851837 HCAPLUS
DOCUMENT NUMBER: 141:104117
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease. [Erratum to document cited in CA136:051990]
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2003), 35(3), 287
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The annotation for the Affymetrix G110 probe set 1770 that was used was incorrect. Although the annotation specifies that the transcript for

PDGFR-α is being ascertained, the true specificity of the probe set is for the PDGFR-β isoform. The ligand for both receptor isoforms is identical. The functional validation of the PDGFR signaling pathway, described in our article, used specific neutralizing antibodies against PDGFR-α as well as downstream small mol. inhibitors, and it implicates this entire cascade. The PDGFR-β isoform may be more relevant in the metastatic process, but this does not discount the proven biol. role of PDGFR-α and downstream effectors in metastatic medulloblastoma.

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(MAPKAP kinase-3-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(N-Shc p52 and p64 isoform-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SHC, N-Shc, p52 and p64 isoforms; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))

IT 9013-66-5, Glutathione peroxidase 9025-26-7, Cathepsin D 9032-68-2, Cathepsin C 37353-41-6, Cysteine protease 80449-02-1, Protein tyrosine kinase 86102-31-0, Tissue inhibitor of metalloproteinase 142008-29-5, CAMP-dependent protein kinase 148348-15-6, Keratinocyte growth factor 149885-84-7, Phosphatase, phosphoprotein (phosphoserine/phosphothreonine/phosphotyrosine) 151769-16-3, TNF-α-converting enzyme 161052-08-0, Gene tie protein kinase 167398-03-0, Protein kinase HEK8 170347-54-3, Gene txk protein kinase 175780-17-3, MAPKAP kinase-3 289898-51-7, JNK1 kinase 377752-08-4, Ribosomal S6 kinase 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))

L20 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:615889 HCAPLUS
DOCUMENT NUMBER: 137:180730
TITLE: Human cDNA/DNA molecules and proteins encoded by them with enhanced expression in apoptosis-resistant cell clones, and use thereof in diagnosis, therapeutics and drug screening
INVENTOR(S): Ullrich, Axel; Abraham, Reimar
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002063037	A2	20020815	WO 2002-EP1073	20020201
WO 2002063037	A3	20031002		
WO 2002063037	A9	20040219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2434881	A1	20020815	CA 2002-2434881		20020201
AU 2002249170	A1	20020819	AU 2002-249170		20020201
AU 2002249170	B2	20070208			
EP 1364066	A2	20031126	EP 2002-718083		20020201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004517638	T	20040617	JP 2002-562773		20020201
US 2004110177	A1	20040610	US 2003-470845		20030731
AU 2007201963	A1	20070524	AU 2007-201963		20070502
PRIORITY APPLN. INFO.:			US 2001-265631P	P	20010202
			AU 2002-249170	A3	20020201
			WO 2002-EP1073	W	20020201

AB The present invention relates to a method for identifying nucleic acid mols. functionally associated with a desired phenotype, such as cancer cell properties, including anti-apoptosis. The method, which allows for generation of expression profiles of genes associated with said desired phenotype, involves a mutagenesis and/or genome rearrangement step, followed by selection of cell clones displaying the desired phenotype. The invention also relates that the method involves the use of the following techniques: fluorescence-activated cell sorting (FACS); nucleic acid microarray (cDNA, genomic or oligonucleotide); protein array; two-dimensional gel electrophoresis; and/or mass spectrometry. The invention further relates that the disclosed method was used to identify genes, which are differentially expressed in apoptosis-sensitive and apoptosis-resistant cells. Specifically, the invention relates that apoptosis was induced in human cervix carcinoma cell line HeLa S3 by Fas activation. After the selection procedure, only a low number of living cells were present, which had a higher resistance against apoptosis than the parental cell line. MRNA was isolated from these surviving clones, and from the parental cell line, and transcribed into cDNA. CDNA microarray technol. was used to identify about 150-200 genes (cDNA/DNA mols.) that exhibited enhanced expression in apoptosis-resistant clones. The GenBank accession nos. of some of these cDNA/DNA mols. are provided, along with the products encoded by said mols. Still further, the invention relates that most of the apoptosis-associated genes encode protein phosphatases, and kinases. Finally, the invention relates that said nucleic acid mols., and proteins encoded by mols., can be used as targets in diagnosis, therapeutics and drug screening, particularly for disorders associated with dysfunction of apoptotic processes, such as tumors.

IT Proteins
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(SHC; identification of proteins (kinases, phosphatases, enzymes, and receptors) with enhanced expression in apoptosis-resistant cell clones, and their use in diagnosis, therapeutics and drug screening)

IT 9001-41-6, Neuroleukin 9001-50-7, Glyceraldehyde-3-phosphate dehydrogenase 9026-43-1, Serine/threonine protein kinase 52660-18-1, Protein kinase ck1 86102-31-0, TIMP 87397-91-9, Thymosin β10 90698-26-3, Ribosomal p70 S6 protein kinase 102925-39-3, β-Adrenergic receptor kinase 124861-55-8, TIMP-2 proteinase inhibitor 127464-60-2, Vascular endothelial growth factor 137632-06-5, Csk tyrosine kinase 137632-07-6, ERK1 protein kinase 140208-22-6, Cdc25B phosphatase 141467-20-1, Wee1 kinase 141760-45-4, Furin 143375-65-9, Cdc2 kinase 144713-50-8, ERK3 protein kinase 145539-86-2,

HCK Tyrosine kinase 146279-87-0 146838-20-2, Gene bcr protein kinase 146838-30-4, MAPKAP kinase-2 147302-47-4, Gene trkC protein tyrosine kinase 148640-14-6, RAC protein kinase 149433-91-0, EphA2 receptor tyrosine kinase 150027-19-3, A-Raf-1 kinase 151662-26-9, Tyrosine kinase itk 152478-57-4, JAK2 protein kinase 152743-99-2, ErbB-4 receptor tyrosine kinase 152787-71-8, Protein kinase TTK 153190-46-6, Protein kinase MLK3 153190-61-5, Tyk2 kinase 154907-65-0, Checkpoint kinase Chk1 154907-68-3, Rse protein tyrosine kinase 156621-09-9, MSK1 protein kinase 156859-16-4, Gene ryk protein kinase 158129-99-8, GRK6 receptor kinase 163441-58-5, Hyl tyrosine kinase 165245-99-8, Protein kinase Plk1 169150-71-4, DAP kinase 170347-50-9, FAST kinase 170780-46-8, Protein tyrosine kinase PYK2 172306-41-1, Protein kinase PCTAIRE-1 172306-53-5, Protein kinase LIMK-1 172308-17-7, Matrix metalloproteinase-15 173585-04-1, Integrin-linked kinase 174206-56-5, Gene mnb protein kinase 175780-17-3, MAPKAP kinase 3 176023-60-2, Gene AKT2 protein kinase 176023-62-4, Protein kinase PKN 178037-70-2, Protein kinase SGK 179466-45-6, Protein kinase Ndr 182238-33-1, Gene RON receptor kinase 182372-11-8, Metalloproteinase ADAM12 184049-62-5, Protein phosphatase PYST1 187042-29-1, Cyclin G-associated kinase 188265-45-4, Gene KHS protein kinase 192230-91-4, MAPK kinase 3 193099-10-4, Metalloprotease ADAM15 194739-73-6, MAP kinase kinase 6 195740-69-3, Protein kinase ARK2 197664-51-0, Gene lok protein kinase 200578-48-9, Protein kinase IRAK-2 202420-94-8, Cdc25C-associated protein kinase 203945-19-1, Protein kinase BUB1 204784-44-1, Protein kinase SRPK2 204934-34-9, EphB3 receptor tyrosine kinase 216974-70-8, EphB4 receptor tyrosine kinase 219575-48-1, Ste20-like kinase 233284-43-0, Gene NEK3 protein kinase 252351-00-1, Metalloprotease ADAM-8 253170-37-5, MSK2 kinase 262450-51-1, Protein kinase MST3 268742-11-6, Protein kinase CHED 300830-60-8, Protein tyrosine phosphatase MEG2 300853-81-0, Protein tyrosine phosphatase ζ 300855-77-0, Protein tyrosine phosphatase 1C 300865-18-3, RPTP-μ 301167-76-0, Protein tyrosine phosphatase CAAX2 327046-95-7, MAP kinase kinase 5 329767-79-5, Protein tyrosine phosphatase σ 335605-46-4, MKK7 protein kinase 335605-46-4, Jun N-terminal kinase kinase 2 352521-00-7, Protein tyrosine phosphatase PRL-3 361186-44-9, Protein phosphatase PP5 362516-16-3, IKKα kinase 366806-33-9, CASEIN KINASE II 408328-74-5, IKKγ kinase 409105-92-6, Protein kinase MAST205 420790-04-1, Pim-2 protein kinase 444993-55-9, Gene VRK1 protein kinase (phosphorylating)
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(identification of proteins (kinases, phosphatases, enzymes, and receptors) with enhanced expression in apoptosis-resistant cell clones, and their use in diagnosis, therapeutics and drug screening)

L20 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:756373 HCAPLUS
DOCUMENT NUMBER: 136:51990
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2001), 29(2), 143-152
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Little is known about the genetic regulation of medulloblastoma

dissemination, but metastatic medulloblastoma is highly associated with poor outcome. We obtained expression profiles of 23 primary medulloblastomas clin. designated as either metastatic (M+) or non-metastatic (M0) and identified 85 genes whose expression differed significantly between classes. Using a class prediction algorithm based on these genes and a leave-one-out approach, we assigned sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with 100% accuracy. We also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably, platelet-derived growth factor receptor α (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway are upregulated in M+ tumors. Immunohistochem. validation on an independent set of tumors shows significant overexpression of PDGFRA in M+ tumors compared to M0 tumors. Using in vitro assays, we show that platelet-derived growth factor α (PDGFA) enhances medulloblastoma migration and increases downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK) and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA blocks MAP2K1, MAP2K2 and MAPK1/3 phosphorylation, whereas U0126, a highly specific inhibitor of MAP2K1 and MAP2K2, also blocks MAPK1/3. Both inhibit migration and prevent PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for PDGFRA and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins should therefore be considered for investigation as possible novel therapeutic strategies against medulloblastoma.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(MAPKAP kinase-3-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(N-Shc p52 and p64 isoform-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SHC, N-Shc, p52 and p64 isoforms; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

IT 9013-66-5, Glutathione peroxidase 9025-26-7, Cathepsin D 9032-68-2, Cathepsin C 37353-41-6, Cysteine protease 80449-02-1, Protein tyrosine kinase 86102-31-0, Tissue inhibitor of metalloproteinase 142008-29-5, CAMP-dependent protein kinase 148348-15-6, Fibroblast growth factor 7 149885-84-7 151769-16-3, TNF-α-converting enzyme 161052-08-0, Gene tie protein kinase 167398-03-0, Protein kinase HEK8 170347-54-3, Gene txk protein kinase 175780-17-3, MAPKAP kinase-3 289898-51-7, JNK1 kinase 377752-08-4, Ribosomal S6 kinase 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

=> d his

(FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007
L1 14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)

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L2          1588 S COLLAGEN AND L1
L3           202 S MINERAL AND L2
L4            67 S COMPOSIT? AND L3
L5            56 DUP REM L4 (11 DUPLICATES REMOVED)
L6             7 S (PORE OR DENSITY OR CM2) AND L5
                 E LI S T/AU
L7           701 S E3
                 E YUEN D/AU
L8            67 S E3
                 E CHEN H C/AU
L9          4244 S E3
L10         5010 S L7 OR L8 OR L9
L11            0 S L3 AND L10

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
L12         1090 S MAPKAP (W)KINASE##
L13         2622 S "MK2"
L14            0 S HEP25/27 (W)KINASE?
L15            0 S HEP25(W)27 (W)KINASE?
L16            0 S HEP25### (W)KINASE?
L17         3551 S L12 OR L13
L18        12206 S "SHC" OR "SRC (W)HOMOLOGY?"
L19           11 S L17 AND L18
L20            8 DUP REM L19 (3 DUPLICATES REMOVED)

=> s "sh2" or "PTB" or "collagen homology domain"
L21       36782 "SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"

=> s l12 and l21
L22            5 L12 AND L21

=> dup rem l22
PROCESSING COMPLETED FOR L22
L23            5 DUP REM L22 (0 DUPLICATES REMOVED)

=> d 1-5 ibib ab

L23  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:388930  HCAPLUS
DOCUMENT NUMBER:          146:455729
TITLE:                    Phosphorylation of Tyr1214 within VEGFR-2 triggers the
                          recruitment of Nck and activation of Fyn leading to
                          SAPK2/p38 activation and endothelial cell migration in
                          response to VEGF. [Erratum to document cited in
                          CA146:020751]
AUTHOR(S):                Lamalice, Laurent; Houle, Francois; Huot, Jacques
CORPORATE SOURCE:         Centre de Recherche en Cancerologie de l'Universite
                          Laval, Quebec, G1R 2J6, Can.
SOURCE:                   Journal of Biological Chemistry (2007), 282(13), 10132
                          CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:                American Society for Biochemistry and Molecular
                          Biology
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   On page 34017, Figure 6B, the image was given incorrectly.  The correct
     figure and legend are given.

L23  ANSWER 2 OF 5  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2006:636793  HCAPLUS
DOCUMENT NUMBER:          145:60928
TITLE:                    Gene expression profiles in the diagnosis of
                          atherosclerosis and in the assessment of the risk of
                          developing the disease
```

INVENTOR(S): West, Mike; Nevins, Joseph R.; Goldschmidt, Pascal; Seo, David
PATENT ASSIGNEE(S): Duke University Office of Science and Technology, USA
SOURCE: U.S. Pat. Appl. Publ., 150 pp., Cont.-in-part of U. S. Ser. No. 291,885.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006141493	A1	20060629	US 2005-198782		20050804
US 2003224383	A1	20031204	US 2002-291885		20021112
PRIORITY APPLN. INFO.:			US 2001-337709P	P	20011109
			US 2002-374547P	P	20020423
			US 2002-420784P	P	20021024
			US 2002-421043P	P	20021025
			US 2002-424680P	P	20021108
			US 2002-291885	A2	20021112
			US 2004-651462P	P	20040804

AB The use of gene expression profiles in the diagnosis of atherosclerosis and in the determination of the risk of development of atherosclerosis is described. These profiles can be used in diagnosis, prophylaxis, and in screening for antiatherosclerotics. Reagents and kits using for detn.of expression profiles of these genes are described. The use of binary prediction tree anal. to correlate expression profile data with other diagnostic information is also described.

L23 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1163769 HCAPLUS
DOCUMENT NUMBER: 146:20751
TITLE: Phosphorylation of Tyr1214 within VEGFR-2 Triggers the Recruitment of Nck and Activation of Fyn Leading to SAPK2/p38 Activation and Endothelial Cell Migration in Response to VEGF
AUTHOR(S): Lamalice, Laurent; Houle, Francois; Huot, Jacques
CORPORATE SOURCE: Centre de Recherche en Cancerologie de l'Universite Laval, Quebec, G1R 2J6, Can.
SOURCE: Journal of Biological Chemistry (2006), 281(45), 34009-34020
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB VEGFR-2 is the major receptor that regulates the different functions of VEGF in adults. We have previously reported that following VEGF treatment of endothelial cells, VEGFR-2 is phosphorylated on Tyr1214 upstream of the Cdc42-SAPK2/p38-MAPKAP K2 pathway. However, little is known of the earliest mol. events that compose the SAPK2/p38 pathway following VEGFR-2 activation. In this study, we address this question using HA-tagged constructs of either wild-type VEGFR-2 or Y1214F VEGFR-2 mutant in immunopptn. assays. We show that the Src family kinase member Fyn, but not c-Src itself, is recruited to VEGFR-2 and is activated in a p.apprx.Tyr1214-dependent manner. We also report that the SH2 domain-containing adapter mol. Nck, but not Grb2, is recruited to VEGFR-2 in ap.apprx.Tyr1214-dependent manner and that it assocs. with Fyn. Moreover, PAK-2 is phosphorylated in a Fyn-dependent manner. Using chemical and genetic inhibitors, we show that Fyn activity is required for SAPK2/p38 but not for FAK activation in response to VEGF. In contrast, c-Src permits activation of FAK, but not that of SAPK2/p38. In addition, Fyn is required for stress fiber formation and endothelial cell migration. We

propose a model in which Fyn forms a mol. complex with Nck and PAK-2 and suggest that this complex assembles in a p.apprx.Tyr1214-dependent manner within VEGFR-2 following VEGF treatment. In turn, this triggers the activation of the SAPK2/p38 MAP kinase module, and promotes stress fiber formation and endothelial cell migration.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:673420 HCAPLUS
DOCUMENT NUMBER: 143:167623
TITLE: Expression profiles of endothelial cells in response to TNF-α, IL-1β, and IL-8, methods of assessing a tissue inflammatory response using the same, and diagnostic and therapeutic uses
INVENTOR(S): Smith, Steven Kevin; Charnock-Jones, David Stephen; Print, Cristin Gregor; Johnson, Nicola Anne
PATENT ASSIGNEE(S): Cambridge University Technical Services Limited, UK
SOURCE: PCT Int. Appl., 492 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005068655	A2	20050728	WO 2005-GB57	20050114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005205218	A1	20050728	AU 2005-205218	20050114
CA 2551677	A1	20050728	CA 2005-2551677	20050114
GB 2424947	A	20061011	GB 2006-15106	20050114
EP 1711630	A2	20061018	EP 2005-701827	20050114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
CN 1934274	A	20070321	CN 2005-80008327	20050114

PRIORITY APPLN. INFO.:		
GB 2004-976	A	20040116
WO 2005-GB57	W	20050114

AB The invention provides methods of assessing a tissue inflammatory response, comprising making a quant. determination of the level of at least five transcripts shown in transcriptome provided in the invention or proteins encoded thereby, in a sample; and comparing the abundance of said transcripts or proteins so determined with the level of said transcript obtained from a control sample. Methods for diagnosis of a condition with which a tissue inflammatory response is associated are also provided, as are gene chip arrays and protein based assays suitable for use in these methods. Assay methods for determining a modulator of a tissue inflammatory response or a condition associated therewith also form part of the invention. The gene expression was profiled in human umbilical vein endothelial cells (HUVEC) contacted with a mixture of TNF-α, interleukin-1β, and interleukin-8. In addition, expression in different endothelial cells types obtained from different parts of the body, namely HUVEC, human coronary artery endothelial cells (HCAEC) and human uterine microvascular

endothelial cells (UtMVEC) were analyzed. It was found that many transcripts were consistently regulated by inflammatory signals in all three cell types.

L23 ANSWER 5 OF 5 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:111797 SCISEARCH
THE GENUINE ARTICLE: 394GN
TITLE: The regulation of protein function by multisite phosphorylation - a 25 year update
AUTHOR: Cohen P (Reprint)
CORPORATE SOURCE: Univ Dundee, MRC, Prot Phosphorylat Unit, MSI WTB Complex, Dundee DD1 5EH, Scotland (Reprint); Univ Dundee, MRC, Prot Phosphorylat Unit, Dundee DD1 5EH, Scotland
COUNTRY OF AUTHOR: Scotland
SOURCE: TRENDS IN BIOCHEMICAL SCIENCES, (DEC 2000) Vol. 25, No. 12, pp. 596-601.
ISSN: 0968-0004.
PUBLISHER: ELSEVIER SCIENCE LONDON, 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 39
ENTRY DATE: Entered STN: 9 Feb 2001
Last Updated on STN: 9 Feb 2001

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The phosphorylation of a protein can alter its behaviour in almost every conceivable way. These include modulation of its intrinsic biological activity, subcellular location, half-life and docking with other proteins. 'Multisite phosphorylation can enable several such effects to operate in the same protein, It can also determine the extent and duration of a response and is the key to signal integration.

=> d his

(FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007

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L1        14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2         1588 S COLLAGEN AND L1
L3          202 S MINERAL AND L2
L4           67 S COMPOSIT? AND L3
L5           56 DUP REM L4 (11 DUPLICATES REMOVED)
L6            7 S (PORE OR DENSITY OR CM2) AND L5
                E LI S T/AU
L7          701 S E3
                E YUEN D/AU
L8           67 S E3
                E CHEN H C/AU
L9         4244 S E3
L10        5010 S L7 OR L8 OR L9
L11           0 S L3 AND L10
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FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007

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L12        1090 S MAPKAP (W)KINASE##
L13        2622 S "MK2"
L14           0 S HEP25/27 (W)KINASE?
L15           0 S HEP25(W)27 (W)KINASE?
L16           0 S HEP25### (W)KINASE?
L17        3551 S L12 OR L13
L18       12206 S "SHC" OR "SRC (W)HOMOLOGY?"
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L19           11 S L17 AND L18
L20            8 DUP REM L19 (3 DUPLICATES REMOVED)
L21        36782 S "SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"
L22            5 S L12 AND L21
L23            5 DUP REM L22 (0 DUPLICATES REMOVED)

=> s l13 and l21
L24            1 L13 AND L21

=> d ibib ab

L24  ANSWER 1 OF 1  SCISEARCH  COPYRIGHT (c) 2007 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2007:347209  SCISEARCH
THE GENUINE ARTICLE: 143PH
TITLE:               Regulation of suppressor of cytokine signaling 3 (SOCS3)
                     mRNA stability by TNF-alpha involves activation of the
                     MKK6/p38(MAPK)/MK2 cascade
AUTHOR:              Ehlting, Christian; Lai, Wi S.; Schaper, Fred;
                     Brenndoerfer, Erwin D.; Matthes, Raphaela-Jessica;
                     Heinrich, Peter C.; Ludwig, Stephan; Blackshear, Perry J.;
                     Gaestel, Matthias; Haeussinger, Dieter; Bode, Johannes G.
                     (Reprint)
CORPORATE SOURCE:    Univ Dusseldorf, Dept Gastroenterol Hepatol & Infectiol,
                     Moorenstr 5, D-4000 Dusseldorf, Germany (Reprint); Univ
                     Dusseldorf, Dept Gastroenterol Hepatol & Infectiol, D-4000
                     Dusseldorf, Germany; Univ Klinikum, Rhein Westfal TH
                     Aachen, Dept Biochem, Aachen, Germany; Univ Munster, Dept
                     Mol Virol, D-4400 Munster, Germany; NIEHS, Lab Neurol,
                     NIH, Res Triangle Pk, NC 27709 USA; NIEHS, Off Clin Res,
                     NIH, Res Triangle Pk, NC 27709 USA; Hannover Med Sch, Dept
                     Biochem, D-3000 Hannover, Germany
                     Johannes.Bode@t-online.de
COUNTRY OF AUTHOR:   Germany; USA
SOURCE:              JOURNAL OF IMMUNOLOGY, (1 MAR 2007) Vol. 178, No. 5, pp.
                     2813-2826.
                     ISSN: 0022-1767.
PUBLISHER:           AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA,
                     MD 20814 USA.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     60
ENTRY DATE:          Entered STN: 5 Apr 2007
                     Last Updated on STN: 5 Apr 2007
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
```

AB The potential of some proinflammatory mediators to inhibit gp130-dependent STAT3 activation by enhancing suppressor of cytokine signaling (SOCS) 3 expression represents an important molecular mechanism admitting the modulation of the cellular response toward gp130-mediated signals. Thus, it is necessary to understand the mechanisms involved in the regulation of SOCS3 expression by proinflammatory mediators. In this study, we investigate SOCS3 expression initiated by the proinflammatory cytokine TNF-alpha. In contrast to IL-6, TNF-alpha increases SOCS3 expression by stabilizing SOCS3 mRNA. Activation of the MAPK kinase 6 (MKK6)/p38(MAPK)-cascade is required for TNF-alpha-mediated stabilization of SOCS3 mRNA and results in enhanced SOCS3 protein expression. In fibroblasts or macrophages deficient for MAPK-activated protein kinase 2 (MK2), a downstream MAPK target of the MKK6/p38(MAPK) cascade, basal SOCS3-expression is strongly reduced and TNF-alpha-induced SOCS3-mRNA stabilization is impaired, indicating that MK2 is crucial for the control of SOCS3 expression by p38(MAPK)-dependent signals. As a target for SOCS3 mRNA stability-regulating signals, a region containing three copies of a pentameric AUUUA motif in close proximity to a U-rich region located between positions 2422 and 2541 of

the 3' untranslated region of SOCS3 is identified. One factor that could target this region is the zinc finger protein tristetraprolin (TTP), which is shown to be capable of destabilizing SOCS3 mRNA via this region. However, data from TTP-deficient cells suggest that TTP does not play an irreplaceable role in the regulation of SOCS3 mRNA stability by TNF-alpha. In summary, these data indicate that TNF-alpha regulates SOCS3 expression on the level of mRNA stability via activation of the MKK6/p38(MAPK) cascade and that the activation of MK2, a downstream target of p38(MAPK), is important for the regulation of SOCS3 expression.

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=> d his

     (FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007
L1         14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2          1588 S COLLAGEN AND L1
L3           202 S MINERAL AND L2
L4            67 S COMPOSIT? AND L3
L5            56 DUP REM L4 (11 DUPLICATES REMOVED)
L6             7 S (PORE OR DENSITY OR CM2) AND L5
                 E LI S T/AU
L7           701 S E3
                 E YUEN D/AU
L8            67 S E3
                 E CHEN H C/AU
L9          4244 S E3
L10         5010 S L7 OR L8 OR L9
L11            0 S L3 AND L10

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
L12         1090 S MAPKAP (W)KINASE##
L13         2622 S "MK2"
L14            0 S HEP25/27 (W)KINASE?
L15            0 S HEP25(W)27 (W)KINASE?
L16            0 S HEP25### (W)KINASE?
L17         3551 S L12 OR L13
L18        12206 S "SHC" OR "SRC (W)HOMOLOGY?"
L19           11 S L17 AND L18
L20            8 DUP REM L19 (3 DUPLICATES REMOVED)
L21        36782 S "SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"
L22            5 S L12 AND L21
L23            5 DUP REM L22 (0 DUPLICATES REMOVED)
L24            1 S L13 AND L21

=> s l13 and l18
L25            5 L13 AND L18

=> d l-5 ibib ab

L25  ANSWER 1 OF 5      MEDLINE on STN
ACCESSION NUMBER:    2004196650      MEDLINE
DOCUMENT NUMBER:     PubMed ID: 15094067
TITLE:               P66(ShcA) interacts with MAPKAP kinase 2 and regulates its
                     activity.
AUTHOR:              Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE:    Department of Inflammation, Wyeth Research, 200 Cambridge
                     Park Drive, Cambridge, MA 02140-2311, USA..
                     yvonne.yannoni@abbott.com
SOURCE:              FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11.
                     Journal code: 0155157. ISSN: 0014-5793.
```

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20 Apr 2004
Last Updated on STN: 4 Jun 2004
Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

L25 ANSWER 2 OF 5 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004171498 EMBASE
TITLE: P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.
AUTHOR: Yannoni Y.M.; Gaestel M.; Lin L.-L.
CORPORATE SOURCE: Y.M. Yannoni, Abbott Bioresearch Center, 100 Research Drive, Worcester, MA 01605, United States. yvonne.yannoni@abbott.com
SOURCE: FEBS Letters, (23 Apr 2004) Vol. 564, No. 1-2, pp. 205-211.
Refs: 41
ISSN: 0014-5793 CODEN: FEBLAL
PUBLISHER IDENT.: S 0014-5793(04)00351-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 May 2004
Last Updated on STN: 6 May 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66 (ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

L25 ANSWER 3 OF 5 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2004-09118 BIOTECHDS
TITLE: New isolated, purified or recombinant protein complex comprising an MK2 polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc for treating or preventing e.g. Crohn's disease, or rheumatoid arthritis;
involving vector-mediated gene transfer and expression in host cell for use in gene therapy

AUTHOR: LIN L; YANNONI Y M
PATENT ASSIGNEE: WYETH
PATENT INFO: WO 2004012660 12 Feb 2004
APPLICATION INFO: WO 2003-US23981 1 Aug 2003
PRIORITY INFO: US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-156998 [15]

AB DERWENT ABSTRACT:

NOVELTY - An isolated, purified or recombinant protein complex comprising a mitogen-activated protein kinase-activated protein kinase 2 (MK2) polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a host cell comprising a first and a second nucleic acid, where the first nucleic acid encodes a recombinant MK2 polypeptide and the second nucleic acid encoding MK2 interacting protein; (2) an assay for determining whether the test compound inhibits or promotes formation of a protein complex; (3) a method for determining whether a test compound affects MK2 activity; (4) an screening assay to identify compounds that inhibit or promote formation of the protein complex; (5) an antibody that binds one or more proteins in the complex; (6) a method for modulating formation of a protein complex in a cell comprising at least a first and a second protein; (7) a method for producing a complex; (8) a drug screening method for identifying anti-inflammatory drugs; (9) a method of modulating inflammation in a tissue; (10) a method of treating or preventing inflammation in a tissue; (11) a method of treating a patient suffering from at least one inflammatory condition; (12) a method of expressing a nucleic acid in a cell to inhibit inflammation; (13) a method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and at least one other kit component chosen from: at least one of buffer and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The fusion protein comprises a domain chosen from affinity tags, radionucleotides, enzymes, and fluorophores. The domain is selected from polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region. Preferred Method: Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test

compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an

MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction, asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

L25 ANSWER 4 OF 5 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:415417 SCISEARCH
THE GENUINE ARTICLE: 815GY
TITLE: P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity
AUTHOR: Yannoni Y M (Reprint); Gaestel M; Lin L L
CORPORATE SOURCE: Abbott Biores Ctr, 100 Res Dr, Worcester, MA 01605 USA (Reprint); Wyeth Res, Dept Inflammat, Cambridge, MA 02140 USA; Hannover Med Sch, Inst Biochem, Hannover, Germany
COUNTRY OF AUTHOR: USA; Germany
SOURCE: FEBS LETTERS, (23 APR 2004) Vol. 564, No. 1-2, pp. 205-211

ISSN: 0014-5793.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41
ENTRY DATE: Entered STN: 21 May 2004
Last Updated on STN: 21 May 2004

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation. (C) 2003 Published by Elsevier B.V. on behalf of the Federation of European Biochemical Societies.

L25 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:120669 HCAPLUS
DOCUMENT NUMBER: 140:175129
TITLE: Mitogen-activated protein kinase-activated protein kinase 2 (MK2) interacting proteins and

therapeutic use in modulating inflamation
INVENTOR(S): Lin, Lih-Ling; Yannoni, Yvonne M.
PATENT ASSIGNEE(S): Wyeth, John, and Brother Ltd., USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004012660	A2	20040212	WO 2003-US23981		20030801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2494577	A1	20040212	CA 2003-2494577		20030801
AU 2003257962	A1	20040223	AU 2003-257962		20030801
EP 1572092	A2	20050914	EP 2003-767026		20030801
EP 1572092	A3	20051207			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
CN 1735687	A	20060215	CN 2003-823700		20030801
JP 2006515159	T	20060525	JP 2004-526272		20030801
US 2006094101	A1	20060504	US 2005-523014		20050201
MX 2005PA01364	A	20050803	MX 2005-PA1364		20050202
IN 2005KN00205	A	20060127	IN 2005-KN205		20050216
PRIORITY APPLN. INFO.:			US 2002-400044P	P	20020802
			WO 2003-US23981	W	20030801

AB The present invention relates to uses of proteins that bind mitogen-activated protein kinase-activated protein kinase 2 (MK2) to modulate inflammation. More particularly, the invention relates to uses of proteins that bind MK2 for treating condition that are related to inflammation. The invention is useful for treating inflammatory conditions, particularly those in which a decrease in inflammation would be therapeutically beneficial.

```
=> s map (w)kinase-activated(w) protein?
L26          492 MAP (W) KINASE-ACTIVATED(W) PROTEIN?

=> d his

     (FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007
L1         14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2          1588 S COLLAGEN AND L1
L3           202 S MINERAL AND L2
L4            67 S COMPOSIT? AND L3
L5            56 DUP REM L4 (11 DUPLICATES REMOVED)
L6             7 S (PORE OR DENSITY OR CM2) AND L5
                 E LI S T/AU
L7           701 S E3
                 E YUEN D/AU
L8            67 S E3
```

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                E CHEN H C/AU
L9          4244 S E3
L10         5010 S L7 OR L8 OR L9
L11            0 S L3 AND L10

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
L12         1090 S MAPKAP (W)KINASE##
L13         2622 S "MK2"
L14            0 S HEP25/27 (W)KINASE?
L15            0 S HEP25(W)27 (W)KINASE?
L16            0 S HEP25### (W)KINASE?
L17         3551 S L12 OR L13
L18        12206 S "SHC" OR "SRC (W)HOMOLOGY?"
L19           11 S L17 AND L18
L20            8 DUP REM L19 (3 DUPLICATES REMOVED)
L21        36782 S "SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"
L22            5 S L12 AND L21
L23            5 DUP REM L22 (0 DUPLICATES REMOVED)
L24            1 S L13 AND L21
L25            5 S L13 AND L18
L26          492 S MAP (W)KINASE-ACTIVATED(W) PROTEIN?

=> s l21 and l26
L27            3 L21 AND L26

=> d 1-3 ibib ab

L27  ANSWER 1 OF 3  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
ACCESSION NUMBER:    2006:680131  BIOSIS
DOCUMENT NUMBER:     PREV200600674553
TITLE:               Phosphorylation of Tyr(1214) within VEGFR-2 triggers the
                     recruitment of Nck and activation of Fyn leading to
                     SAPK2/p38 activation and endothelial cell migration in
                     response to VEGF.
AUTHOR(S):           Lamalice, Laurent; Houle, Francois; Huot, Jacques [Reprint
                     Author]
CORPORATE SOURCE:    Univ Laval, Hotel Dieu, Ctr Rech Cancerol, 9 Rue McMahon,
                     Quebec City, PQ G1R 2J6, Canada
                     Jacques.Huot@phc.ulaval.ca
SOURCE:              Journal of Biological Chemistry, (NOV 10 2006) Vol. 281,
                     No. 45, pp. 34009-34020.
                     CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE:       Article
LANGUAGE:            English
ENTRY DATE:          Entered STN: 6 Dec 2006
                     Last Updated on STN: 6 Dec 2006
AB   VEGFR-2 is the major receptor that regulates the different functions of
     VEGF in adults.  We have previously reported that following VEGF treatment
     of endothelial cells, VEGFR-2 is phosphorylated on Tyr1214 upstream of the
     Cdc42-SAPK2/p38MAPKAP K2 pathway.  However, little is known of the
     earliest molecular events that compose the SAPK2/p38 pathway following
     VEGFR-2 activation.  In this study, we address this question using
     HA-tagged constructs of either wild-type VEGFR-2 or Y1214F VEGFR-2 mutant
     in immunoprecipitation assays.  We show that the Src family kinase member
     Fyn, but not c-Src itself, is recruited to VEGFR-2 and is activated in a p
     similar to Tyr(1214)-dependent manner.  We also report that the
     SH2 domain-containing adapter molecule Nck, but not Grb2, is
     recruited to VEGFR-2 in a p similar to Tyr1214-dependent manner and that
     it associates with Fyn.  Moreover, PAK-2 is phosphorylated in a
     Fyn-dependent manner.  Using chemical and genetic inhibitors, we show that
     Fyn activity is required for SAPK2/p38 but not for FAK activation in
     response to VEGF.  In contrast, c-Src permits activation of FAK, but not
     that of SAPK2/p38.  In addition, Fyn is required for stress fiber
```

formation and endothelial cell migration. We propose a model in which Fyn forms a molecular complex with Nck and PAK-2 and suggest that this complex assembles in a p similar to Tyr(1214)-dependent manner within VEGFR-2 following VEGF treatment. In turn, this triggers the activation of the SAPK2/p38 MAP kinase module, and promotes stress fiber formation and endothelial cell migration.

L27 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:710876 HCAPLUS
DOCUMENT NUMBER: 145:161778
TITLE: Identification of phospholipase A2 as target in cancer treatment, with special emphasis on colorectal cancer and its mechanism of action
INVENTOR(S): Scherer, Andreas; Papoian, Ruben
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006076414	A2	20060720	WO 2006-US953	20060112
WO 2006076414	A3	20070322		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-643990P P 20050114
AB A peptide GPA071 of phospholipase A2 had been detected in human plasma and synthesized. The phospholipase A2 peptide GPA071 was injected into mice and gene expression profiling on many organs performed. Phospholipase A2 showed significant effects on regulation of gene expression in the liver. The genes affected are members of the integrin signaling pathway, wnt pathway and PTEN pathway. The changes in gene expression indicate a pos. effect of phospholipase A2 on cell proliferation and invasiveness. The gene annotation points at colorectal cancer.

L27 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:397093 HCAPLUS
DOCUMENT NUMBER: 131:165705
TITLE: Diverse signaling pathways activated by growth factor receptors induce broadly overlapping, rather than independent, sets of genes
AUTHOR(S): Fambrough, Douglas; McClure, Kimberly; Kazlauskas, Andrius; Lander, Eric S.
CORPORATE SOURCE: Nine Cambridge Center, Whitehead Institute for Biomedical Research, Cambridge, MA, 02142, USA
SOURCE: Cell (Cambridge, Massachusetts) (1999), 97(6), 727-741
CODEN: CELLB5; ISSN: 0092-8674
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We sought to explore the relationship between receptor tyrosine kinase

(RTK) activated signaling pathways and the transcriptional induction of immediate early genes (IEGs). Using global expression monitoring, we identified 66 fibroblast IEGs induced by platelet-derived growth factor β receptor (PDGFRβ) signaling. Mutant receptors lacking binding sites for activation of the PLCγ, PI3K, SHP2, and RasGAP pathways still retain partial ability to induce 64 of these IEGs. Removal of the Grb2-binding site further broadly reduces induction. These results suggest that the diverse pathways exert broadly overlapping effects on IEG induction. Interestingly, a mutant receptor that restores the RasGAP-binding site promotes induction of an independent group of genes, normally induced by interferons. Finally, we compare the PDGFRβ and fibroblast growth factor receptor 1; each induces essentially identical IEGs in fibroblasts.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d 3 kwic

L27  ANSWER 3 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
IT   Proteins, specific or class
     RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL
     (Biological study); FORM (Formation, nonpreparative)
        (Cish (cytokine inducible SH2-containing protein); growth factor
        receptor activation of diverse signaling pathways and induction of
        broadly overlapping gene expression)
IT   9035-51-2, Cytochrome P 450, biological studies   9035-58-9,
     Blood-coagulation factor III   9054-89-1, Superoxide dismutase
     37205-35-9, Arginyl tRNA synthetase   79747-53-8, Phosphotyrosine
     phosphatase   127464-60-2, Vascular endothelial growth factor
     140208-23-7, Plasminogen Activator Inhibitor 1   140208-24-8, TIMP 1
     143180-75-0   146838-30-4, MAP kinase-
     activated protein kinase 2   148348-15-6, Fibroblast
     growth factor 7   154531-34-7   154835-90-2, Adrenomedullin   178037-70-2,
     Gene sgk protein kinase   189460-40-0, Connective tissue growth factor
     196717-71-2, Epiregulin
     RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL
     (Biological study); FORM (Formation, nonpreparative)
        (growth factor receptor activation of diverse signaling pathways and
        induction of broadly overlapping gene expression)


=> e yannoni y/au
E1            1     YANNONI NINO/AU
E2            2     YANNONI S/AU
E3           16 --> YANNONI Y/AU
E4           14     YANNONI Y M/AU
E5            7     YANNONI YVONNE/AU
E6           11     YANNONI YVONNE M/AU
E7            1     YANNONL COSTANTINO S/AU
E8            1     YANNONNI C S/AU
E9           42     YANNOPAPAS V/AU
E10          11     YANNOPAPAS VASSILIOS/AU
E11           1     YANNOPAPAS VASSILIS/AU
E12           1     YANNOPOLOS J C/AU

=> s e3-e6
L28          48 ("YANNONI Y"/AU OR "YANNONI Y M"/AU OR "YANNONI YVONNE"/AU OR
                "YANNONI YVONNE M"/AU)

=> e lin l l/au
E1          131     LIN L K/AU
E2            1     LIN L KH/AU
E3          521 --> LIN L L/AU
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E4            1      LIN L L J/AU
E5          169      LIN L L K/AU
E6            2      LIN L L L/AU
E7            1      LIN L L Y/AU
E8          377      LIN L M/AU
E9            1      LIN L M P/AU
E10           1      LIN L MICHAEL/AU
E11         139      LIN L N/AU
E12         190      LIN L P/AU

=> s e3
L29         521 "LIN L L"/AU

=> s l28 or 129
L30         565 L28 OR L29

=> d his

     (FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007
L1         14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2          1588 S COLLAGEN AND L1
L3           202 S MINERAL AND L2
L4            67 S COMPOSIT? AND L3
L5            56 DUP REM L4 (11 DUPLICATES REMOVED)
L6             7 S (PORE OR DENSITY OR CM2) AND L5
                 E LI S T/AU
L7           701 S E3
                 E YUEN D/AU
L8            67 S E3
                 E CHEN H C/AU
L9          4244 S E3
L10         5010 S L7 OR L8 OR L9
L11            0 S L3 AND L10

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
L12         1090 S MAPKAP (W)KINASE##
L13         2622 S "MK2"
L14            0 S HEP25/27 (W)KINASE?
L15            0 S HEP25(W)27 (W)KINASE?
L16            0 S HEP25### (W)KINASE?
L17         3551 S L12 OR L13
L18        12206 S "SHC" OR "SRC (W)HOMOLOGY?"
L19           11 S L17 AND L18
L20            8 DUP REM L19 (3 DUPLICATES REMOVED)
L21        36782 S "SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"
L22            5 S L12 AND L21
L23            5 DUP REM L22 (0 DUPLICATES REMOVED)
L24            1 S L13 AND L21
L25            5 S L13 AND L18
L26          492 S MAP (W)KINASE-ACTIVATED(W) PROTEIN?
L27            3 S L21 AND L26
                 E YANNONI Y/AU
L28           48 S E3-E6
                 E LIN L L/AU
L29          521 S E3
L30          565 S L28 OR L29

=> s l18 and l30
L31            5 L18 AND L30
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=> dup rem l31
PROCESSING COMPLETED FOR L31
L32             2 DUP REM L31 (3 DUPLICATES REMOVED)

=> d 1-2 ibib ab

L32   ANSWER 1 OF 2  BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
      DUPLICATE 1
ACCESSION NUMBER: 2004-09118  BIOTECHDS
TITLE:            New isolated, purified or recombinant protein complex
                  comprising an MK2 polypeptide, and an MK2 interacting protein
                  chosen from STS, HPH2 and Shc for treating or
                  preventing e.g. Crohn's disease, or rheumatoid arthritis;
                     involving vector-mediated gene transfer and expression in
                     host cell for use in gene therapy
AUTHOR:           LIN L; YANNONI Y M
PATENT ASSIGNEE:  WYETH
PATENT INFO:      WO 2004012660 12 Feb 2004
APPLICATION INFO: WO 2003-US23981 1 Aug 2003
PRIORITY INFO:    US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002
DOCUMENT TYPE:    Patent
LANGUAGE:         English
OTHER SOURCE:     WPI: 2004-156998 [15]
AB    DERWENT ABSTRACT:
      NOVELTY - An isolated, purified or recombinant protein complex comprising
      a mitogen-activated protein kinase-activated protein kinase 2 (MK2)
      polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and
      Shc, is new.
           DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the
      following: (1) a host cell comprising a first and a second nucleic acid,
      where the first nucleic acid encodes a recombinant MK2 polypeptide and
      the second nucleic acid encoding MK2 interacting protein; (2) an assay
      for determining whether the test compound inhibits or promotes formation
      of a protein complex; (3) a method for determining whether a test
      compound affects MK2 activity; (4) an screening assay to identify
      compounds that inhibit or promote formation of the protein complex; (5)
      an antibody that binds one or more proteins in the complex; (6) a method
      for modulating formation of a protein complex in a cell comprising at
      least a first and a second protein; (7) a method for producing a complex;
      (8) a drug screening method for identifying anti-inflammatory drugs; (9)
      a method of modulating inflammation in a tissue; (10) a method of
      treating or preventing inflammation in a tissue; (11) a method of
      treating a patient suffering from at least one inflammatory condition;
      (12) a method of expressing a nucleic acid in a cell to inhibit
      inflammation; (13) a method of detecting at least one of the absence,
      presence and amount of MK2 in a sample; (14) a kit that enables
      qualitative detection of MK2 comprising a compound that interacts with at
      least one of MK2 or an MK2 complex, where the compound is chosen from an
      antibody, a chemical agent, a small molecule, a protein and a peptide;
      and at least one other kit component chosen from: at least one of buffer
      and solution; and at least one structural component; and (15) a
      pharmaceutical composition comprising at least one protein that binds
      MK2, and at least one carrier.
           BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an
      MK2 polypeptide and at least one or two MK2 interacting protein. The MK2
      interacting protein is chosen from STS, HPH2 and Shc. The MK2
      polypeptide comprises a fusion protein. The fusion protein comprises a
      domain for purifying, isolating or detecting the fusion protein. The
      fusion protein comprises a domain chosen from affinity tags,
      radionucleotides, enzymes, and fluorophores. The domain is selected from
      polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST),
      thioredoxin, protein A, protein G, and an immunoglobulin heavy chain
      constant region. Preferred Method: Determining whether a test compound
      inhibits or promotes formation of a protein complex comprises forming a
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reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2-interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or

peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction, asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

L32 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER:	2004196650 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 15094067
TITLE:	P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.
AUTHOR:	Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE:	Department of Inflammation, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140-2311, USA.. yvonne.yannoni@abbott.com
SOURCE:	FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY:	Netherlands
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200406
ENTRY DATE:	Entered STN: 20 Apr 2004 Last Updated on STN: 4 Jun 2004 Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

=> d his

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     (FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007
L1         14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2          1588 S COLLAGEN AND L1
L3           202 S MINERAL AND L2
L4            67 S COMPOSIT? AND L3
L5            56 DUP REM L4 (11 DUPLICATES REMOVED)
L6             7 S (PORE OR DENSITY OR CM2) AND L5
                 E LI S T/AU
L7           701 S E3
                 E YUEN D/AU
L8            67 S E3
                 E CHEN H C/AU
L9          4244 S E3
L10         5010 S L7 OR L8 OR L9
L11            0 S L3 AND L10

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007
L12         1090 S MAPKAP (W)KINASE##
L13         2622 S "MK2"
L14            0 S HEP25/27 (W)KINASE?
L15            0 S HEP25(W)27 (W)KINASE?
L16            0 S HEP25### (W)KINASE?
L17         3551 S L12 OR L13
L18        12206 S "SHC" OR "SRC (W)HOMOLOGY?"
L19           11 S L17 AND L18
L20            8 DUP REM L19 (3 DUPLICATES REMOVED)
L21        36782 S "SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"
L22            5 S L12 AND L21
L23            5 DUP REM L22 (0 DUPLICATES REMOVED)
L24            1 S L13 AND L21
L25            5 S L13 AND L18
L26          492 S MAP (W)KINASE-ACTIVATED(W) PROTEIN?
L27            3 S L21 AND L26
                 E YANNONI Y/AU
L28           48 S E3-E6
                 E LIN L L/AU
L29          521 S E3
L30          565 S L28 OR L29
L31            5 S L18 AND L30
L32            2 DUP REM L31 (3 DUPLICATES REMOVED)

=> s l21 and yeast?
L33         1465 L21 AND YEAST?

=> s l13 and l33
L34            0 L13 AND L33

=> s l17 and l33
L35            0 L17 AND L33

=> s l18 and (interact or bind? or attach?)
   5 FILES SEARCHED...
L36         5973 L18 AND (INTERACT OR BIND? OR ATTACH?)

=> s l33 and l36
L37          167 L33 AND L36

=> dup rem l37
PROCESSING COMPLETED FOR L37
L38           49 DUP REM L37 (118 DUPLICATES REMOVED)
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=> d 1-49 ibib ab

L38 ANSWER 1 OF 49 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2006-14057 BIOTECHDS
TITLE: Determining genotoxicity of test compound, by contacting test cell with test compound, and determining change in expression level of an indicator gene, where increased expression indicates that the compound exhibits genotoxicity; determination of genotoxicity of a compound using a transgenic animal expressing a reporter gene useful for a drug screening application
AUTHOR: ALLARD J D; AUD D; LIAO G; PELTZ G A
PATENT ASSIGNEE: ROCHE PALO ALTO LLC
PATENT INFO: US 2006110768 25 May 2006
APPLICATION INFO: US 2005-286216 23 Nov 2005
PRIORITY INFO: US 2005-286216 23 Nov 2005; US 2004-630672 24 Nov 2004
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2006-363176 [37]
AB DERWENT ABSTRACT:

NOVELTY - Determining the genotoxicity of a test compound comprising contacting a viable test cell with the test compound, and determining the change in expression level of an indicator gene, where an increase in expression of at least 1.5-fold indicates that the test compound exhibits genotoxicity, is new.

DETAILED DESCRIPTION - Determining the genotoxicity of a test compound comprises: (a) contacting a viable test cell with the test compound; and (b) determining the change in expression level of an indicator gene selected from Prelp (Proline arginine-rich end leucine-rich repeat); Sesn2 (Sestrin 2); 4833427G06 Rik (RIKEN cDNA); Dda3 (Differential display and activated by p53); Usp30 (Ubiquitin specific protease 30); 0610013D04 Rik (RIKEN cDNA); Slc19a2 (Solute carrier family 19 (thiamine transporter), member 2); Trp53inp1 (Transformation related protein 53, inducible nuclear protein 1); D4Ertd421e (DNA segment, Chr 4, ERATO Doi 421, expressed); Shcbp1 (Shc SH2-domain binding protein 1); Mki67 (Antigen identified by MAb Ki67); Phex (Phosphate regulating neutral endopeptidase (X chromosome)); Tk1 (Thymidine kinase 1); Mmhead (Mus musculus 15 day embryo head cDNA clone); Osbp16 (Oxysterol binding protein-like 6); Mphosph1 (M-phase phosphoprotein); Ephx1 (Epoxide hydrolase 1 (microsomal xenobiotic hydrolase)); Top2a (Topoisomerase (DNA) II alpha); Ccng1 (Cyclin G1); Plf (Proliferin); Np95 (Nuclear protein 95); Rad51ap1 (RAD51-associated protein 1); Nos3 (Nitric oxide synthase 3, endothelial cell); 2610005B21 Rik (RIKEN cDNA); Brca1 (Breast cancer 1); Stk18 (Serine/threonine kinase 18); Calmbp1 (Calmodulin binding protein 1); Lek1 (Leucine, glutamic acid, lysine family 1 protein); Smc2l1 (SMC2 structural maintenance of chromosomes 2-like 1); E2f-/(E2F transcription factor 7); Hmmr (Hyaluronan mediated motility receptor (RHAMM)); Nusap1 (Nucleolar and spindle associated protein 1); Fbxo5 (f-box only protein 31); Slc19a2 (Solute carrier family 19 (thiamine transporter), member 2); 9030617003 Rik (RIKEN cDNA); Ly6e (Lymphocyte antigen 6 complex, locus E); 6530401L14 Rik (RIKEN cDNA); Mad3 (Max dimerization protein 3); Hmgb2 (High mobility group box 2); Kif11 (Kinesin 11); Mad2l1 (MAD2 (mitotic arrest deficient, homolog)-like 1 (yeast)); Asf1b (ASF1 anti-silencing function 1 homolog B (Saccharomyces)); Mcm3 (Minichromosome maintenance deficient 3 (Saccharomyces)); MGC: 32192 (Mus musculus cDNA clone MGC:32192 IMAGE:5006129); Foxm1 (Forkhead box M1); Anxa8 (Annexin A8); Slc35a5 (Solute carrier family 35, member A5); E030024M05 Rik (RIKEN cDNA); Cks2 (CDC28 protein kinase regulatory subunit 2); Cilp (Cartilage intermediate layer pro); Tacc3 (Transforming, acidic coiled-coil containing protein 3); Prc1 (Protein regulator of cytokinesis 1); 2610509G12 Rik (RIKEN cDNA); 2810417H13 Rik (RIKEN cDNA);

Pbk (PDZ binding kinase); Capn6 (Calpain 6); Gmnn (Geminln); Mcmd4 (Minichromosome maintenance deficient 4 homolog); Ccna2 (Cyclin A2); Pola1 (DNA polymerase alpha 1, 180 kDa); Hmgb3 (High mobility group box 3); Tagln (Transgelin (smooth muscle 22 protein)); 1600013K19 Rik (RIKEN cDNA); Serpine1 (Ser (or Cys) proteinase inhibitor, clade E, member 1); Wig1 (Wild-type p53-induced gene 1); Hgf (Hepatocyte growth factor (scatter factor)); Gnpi (Glucosamine-6-phosphate deaminase); Birc5 (Baculoviral IAP repeat-containing 5); Prim1 (DNA primase, p49 subunit); Rbl1 (Retinoblastoma-like 1 (p107)); Pcna (Proliferating cell nuclear antigen); E130315B21 Rik (RIKEN cDNA); 2610019103 RIK (RIKEN cDNA), where an increase in expression of at least 1.5-fold indicates that the test compound exhibits genotoxicity. An INDEPENDENT CLAIM is also included for a non-human transgenic animal, comprising a reporter gene operatively linked to a Dog1 promoter.

WIDER DISCLOSURE - (1) a kit for determining the genotoxicity of a test compound comprising a cell capable of differentiation, and reagents for quantifying the expression levels of selected indicator genes; (2) a polynucleotide capable of specifically hybridizing to a polynucleotide comprising fully defined 336-808 base pair sequences (SEQ ID NO: 5, 7, 9, 11, 13, 15, or 17) given in the specification, or its complement; (3) a set of polynucleotides capable of specifically hybridizing to the selected indicator genes; (4) a microarray comprising a set of polynucleotides capable of specifically hybridizing to the selected indicator genes; (5) a polypeptide comprising fully defined 112-168 amino acid sequences (SEQ ID NO: 6, 8, 10, 12, 14, 16, or 18) given in the specification; and (6) an antibody capable of specifically binding to the polypeptide of SEQ ID NO: 6, 8, 10, 12, 14, 16, or 18.

BIOTECHNOLOGY - Preferred Method: In determining the genotoxicity of a test compound, the indicator gene is selected from 4833427G06Rik or Dda3. The test cell comprises a myoblast cell. It is also selected from mouse, rat, zebrafish, human, chimpanzee, or chicken blast cells. Determining the change in expression level comprises measuring the amount of mRNA produced using RT-PCR, or comprises measuring the increase in signal produced by increased expression of a label.

USE - The method is useful for determining the genotoxicity of a test compound.

EXAMPLE - No relevant example given.(38 pages)

L38 ANSWER 2 OF 49 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2006595377 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16647839
TITLE: Dok5 is substrate of TrkB and TrkC receptors and involved in neurotrophin induced MAPK activation.
AUTHOR: Shi Lei; Yue Jiping; You Yuangang; Yin Bin; Gong Yanhua; Xu Caimin; Qiang Boqin; Yuan Jiangang; Liu Yongjian; Peng Xiaozhong
CORPORATE SOURCE: The National Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, Chinese National Human Genome Center, Beijing 100005, China.
SOURCE: Cellular signalling, (2006 Nov) Vol. 18, No. 11, pp. 1995-2003. Electronic Publication: 2006-05-02. Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200704
ENTRY DATE: Entered STN: 11 Oct 2006
Last Updated on STN: 11 Apr 2007
Entered Medline: 10 Apr 2007

AB Tropomyosin-related kinase (Trk) family receptors are a group of high

affinity receptors for neurotrophin growth factors, which have pivotal functions in many physiological processes of nervous system. Trk receptors can dimerize and autophosphorylate upon neurotrophin stimulation, then recruit multiple adaptor proteins to transduct signal. In this report, we identified Dok5, a member of Dok family, as a new substrate of TrkB/C receptors. In yeast two-hybrid assay, Dok5 can interact with intracellular domain of TrkB and TrkC receptor through its PTB domain, but not with that of TrkA receptor. The interaction was then confirmed by GST pull-down assay and Co-IP experiment. Dok5 co-localized with TrkB and TrkC in differentiated PC12 cells, providing another evidence for their interaction. By using mutational analysis, we characterized that Dok5 PTB domain bound to Trk receptor NPQY motif in a kinase-activity-dependent manner. Furthermore, competition experiment indicated that Dok5 competed with N-shc for binding to the receptors at the same site.
Finally, we showed that Dok5 was involved in the activation of MAPK pathway induced by neurotrophin stimulation. Taken together, these results suggest that Dok5 acts as substrate of TrkB/C receptors and is involved in neurotrophin induced MAPK signal pathway activation.

L38 ANSWER 3 OF 49 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2006085565 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16126371
TITLE: Disruption of ShcA signaling halts cell proliferation--characterization of ShcC residues that influence signaling pathways using yeast.
AUTHOR: Heinrich Julia N; Kwak Seung P; Howland David S; Chen Jin; Sturner Stephen; Sullivan Kelly; Lipinski Kerri; Cheng Ke-Yi; She Yijin; Lo Frederick; Ghavami Afshin
CORPORATE SOURCE: Neuroscience Discovery Research, Wyeth Research, 865 Ridge Road, Monmouth Junction, New Jersey 08852-2718, USA.. heinrij@wyeth.com
SOURCE: Cellular signalling, (2006 Jun) Vol. 18, No. 6, pp. 795-806. Electronic Publication: 2005-08-26. Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200606
ENTRY DATE: Entered STN: 14 Feb 2006
Last Updated on STN: 10 Jun 2006
Entered Medline: 9 Jun 2006

AB Shc adapter proteins are thought to regulate cellular proliferation, differentiation and apoptosis by activating the SOS-Grb2-RAS-MAPK signaling cascade. Using the small hairpin RNA (shRNA) technique, we found that decreasing ShcA mRNA reduced the proliferative ability of HEK293 mammalian culture cells. We then recapitulated phosphorylation-dependent Shc-Grb2 complex formation in Saccharomyces cerevisiae. Immunoprecipitation followed by Western analysis demonstrated that activated TrkB, composed of the intracellular domain of TrkB fused to glutathione S-transferase (GST-TrkB(ICD)), promoted the association of ShcC and Grb2 in yeast. The Ras-recruitment system (RRS), in which a myristoylated (Myr)-bait and son of sevenless (hSOS)-prey are brought together to complement the defective Ras-cAMP pathway in a thermosensitive cdc25H mutant yeast strain, was used to validate a phenotypic assay. Yeast cells transformed with both Myr-ShcC and hSOS-Grb2 (referred to as scheme 1) or Myr-Grb2 and hSOS-ShcC (scheme 2) did not grow at non-permissive temperature; the additional transformation of GST-TrkB(ICD) enabled growth. GST-TrkB(ICD) also enabled growth with hSOS-Grb2 and either Myr-ShcA or Myr-SHP2. Mutational analysis of TrkB showed that its kinase activity was essential for complementation, while its docking site for Shc proteins was not. Mutational analysis of ShcC showed that the

PTB and SH2 domains were not essential for complementation but phosphorylation at Y304 in the CH1 domain was. Phosphorylation at Y304 could not be substituted by an acidic amino acid. The RRS provides a genetic system to probe Shc proteins and potentially identify member specific protein partners and pharmacological reagents.

L38 ANSWER 4 OF 49 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:451135 HCAPLUS
DOCUMENT NUMBER: 143:2238
TITLE: Genes differentially expressed by neural progenitor cells of the human white matter
INVENTOR(S): Goldman, Steven A.; Fraser, Sim
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005046610	A2	20050526	WO 2004-US37669	20041110
WO 2005046610	A3	20070524		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, AP, EA, EP, OA				
CA 2547474	A1	20050526	CA 2004-2547474	20041110
US 2005176626	A1	20050811	US 2004-985306	20041110
EP 1684706	A2	20060802	EP 2004-818696	20041110
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU				

PRIORITY APPLN. INFO.: US 2003-519310P P 20031110
WO 2004-US37669 W 20041110

AB The present invention relates to a method of modulating production of neurons and/or oligodendrocytes from neural progenitor cells of human white matter and to a method of treating a subject for a condition modulated by underprodn. of oligodendrocytes from human white matter. Both of these methods involve administering an agonist or antagonist of one or more mols. set forth in Tables 1 and/or 2 to the neural progenitor cells. Also disclosed is a method of using an inhibitor of sterol synthesis to differentiate oligodendrocyte progenitor cells to oligodendrocytes. To identify genes that regulate both the turnover and fate decisions of adult glial progenitor cell population in vivo, U95Av2 Affymetrix microarrays were used to analyze the transcriptional profile of A2B5+ white matter progenitor cells (WMPCs), sorted from human white matter samples derived from surgically-resected adult temporal lobe. The profile of each sorted cell population was then normalized against that of the unsorted dissociate from which it was derived, to identify WMPC-enriched transcripts that were otherwise underrepresented in the white matter. By this strategy, several unexpected ligands and receptors and their attendant signaling pathways were identified that appear to uniquely characterize the interaction of oligodendrocyte progenitor cells with the ambient white matter in which they reside.

L38 ANSWER 5 OF 49 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:324396 HCAPLUS
DOCUMENT NUMBER: 142:387156
TITLE: Sixty-two markers up- or down-regulated in breast cancer patients, and related gene expression profiling for breast cancer classification and prognosis
INVENTOR(S): Yu, Kun; Tan, Patrick
PATENT ASSIGNEE(S): NCC Technology Ventures Pte. Limited, Singapore; Forrest, Graham
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005033699	A2	20050414	WO 2004-GB4195	20041001
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1668357	A2	20060614	EP 2004-768735	20041001
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2007508812	T	20070412	JP 2006-530583	20041001
US 2007059706	A1	20070315	US 2006-574392	20061122
PRIORITY APPLN. INFO.:			GB 2003-23225 A	20031003
			WO 2004-GB4195 W	20041001

AB The inventors set out to identify a set of genes for use as prognostic markers for breast tumors which correlate with the Nottingham Prognostic Index (NPI). Initially they were unable to identify a single set of genes whose expression correlates with the NPI. However after segregating the dataset into mol. subcategories (estrogen receptor pos., estrogen receptor neg., and ErbB2 pos.) they identified a set of 62 genes which are differentially expressed in tumors of different prognoses. Methods and apparatus for determining prognosis are provided. Also provided are methods of determining the response of tumors to chemotherapy involving comparing the expression levels of the predictive gene set before and after treatment.

L38 ANSWER 6 OF 49 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1020555 HCAPLUS
DOCUMENT NUMBER: 143:320266
TITLE: Genes with differential expression profile between human dental pulp stem cells and mesenchymal stem cells and use for regenerating tooth germ
INVENTOR(S): Ueda, Minoru; Yamada, Yoichi
PATENT ASSIGNEE(S): Hitachi Medical Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 246 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2005253442	A	20050922	JP 2004-111582	20040309
PRIORITY APPLN. INFO.:			JP 2004-111582	20040309

AB The present invention relates to a group of genes whose expression profile are different between human dental pulp stem cells and mesenchymal stem cells, as well as a method for regenerating tooth germ using these genes. According to the present invention, the gene expression profiles and cluster anal. between human dental pulp stem cells (hDPSCs) and mesenchymal stem cells (hMSCs) as representative populations of odontoprogenitor and osteoprogenitor cell were revealed, and a group of genes whose expression profile are different between human dental pulp stem cells and mesenchymal stem cells was identified. By utilizing the groups of the genes of the present invention together with the dental pulp stem cells and mesenchymal stem cells, hard tissue such as tooth germ, dental pulp, dentin or bone can be regenerated. The present inventors investigated the gene expression profiles and cluster anal. between human dental pulp stem cells (hDPSCs) and mesenchymal stem cells (hMSCs) as representative populations of odontoprogenitor and osteoprogenitor cells, resp. At first, the present inventors confirmed the differential expression of Alkaline phosphatase (ALP) activity, Dentin matrix protein 1 (DMP 1), Dentin phosphosialoprotein (DSPP) using by real time reverse-transcriptase polymerase chain reaction (RT-PCR) in total RNA from primary cultures. The number of genes in hDPSCs(I) that were up-regulated by 2>-fold, compared to hMSCs, was 614 (Table, IV). On the other band, the number of genes down regulated by <2-fold in hDPSCs (I) was 296 (Table III, IV).

L38 ANSWER 7 OF 49 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 3

ACCESSION NUMBER: 2005584646 EMBASE
TITLE: SLAM-associated protein as a potential negative regulator in Trk signaling.
AUTHOR: Lo K.Y.; Chin W.H.; Ng Y.P.; Cheng A.W.; Cheung Z.H.; Ip N.Y.
CORPORATE SOURCE: N.Y. Ip, Dept. of Biochemistry, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, Hong Kong. BOIP@UST.HK
SOURCE: Journal of Biological Chemistry, (16 Dec 2005) Vol. 280, No. 50, pp. 41744-41752. .
Refs: 35
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jan 2006
Last Updated on STN: 19 Jan 2006

AB Neurotrophin signaling plays important roles in regulating the survival, differentiation, and maintenance of neurons in the nervous system. Binding of neurotrophins to their cognate receptors Trks induces transactivation and phosphorylation of the receptor at several tyrosine residues. These phosphorylated tyrosine residues then serve as crucial docking sites for adaptor proteins containing a Src homology 2 or phosphotyrosine binding domain, which upon association with the receptor initiates multiple signaling events to mediate the action of neurotrophins. Here we report the identification of a Src homology 2 domain-containing molecule, SLAM-associated protein (SAP), as an interacting protein of TrkB in a yeast two-hybrid screen. SAP was initially identified as an adaptor molecule in SLAM family receptor signaling for regulating interferon-γ secretion. In the current study, we found that SAP interacted with TrkA, TrkB, and TrkC receptors in

vitro and in vivo. Binding of SAP required Trk receptor activation and phosphorylation at the tyrosine 674 residue, which is located in the activation loop of the kinase domain. Overexpression of SAP with Trk attenuated tyrosine phosphorylation of the receptors and reduced the binding of SH2B and She to TrkB. Moreover, overexpression of SAP in PC12 cells suppressed the nerve growth factor-dependent activation of extracellular signal-regulated kinases 1/2 and phospholipase Cγ, in addition to inhibiting neurite outgrowth. In summary, our findings demonstrated that SAP may serve as a negative regulator of Trk receptor activation and downstream signaling. .COPYRGT. 2005 by The American Society for Biochemistry and Molecular Biology, Inc.

L38 ANSWER 8 OF 49 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2005280250 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15924411
TITLE: Identification of a NPXY motif in growth factor receptor-bound protein 14 (Grb14) and its interaction with the phosphotyrosine-binding (PTB) domain of IRS-1.
AUTHOR: Rajala Raju V S; Chan Michael D
CORPORATE SOURCE: Department of Cell Biology, University of Oklahoma Health Sciences Center, and Dean A. McGee Eye Institute, Oklahoma City, Oklahoma 73104, USA.. raju-rajala@ouhsc.edu
CONTRACT NUMBER: EY00871 (NEI)
EY04149 (NEI)
EY12190 (NEI)
RR17703 (NCRR)
SOURCE: Biochemistry, (2005 Jun 7) Vol. 44, No. 22, pp. 7929-35. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AY772475
ENTRY MONTH: 200508
ENTRY DATE: Entered STN: 1 Jun 2005
Last Updated on STN: 27 Aug 2005
Entered Medline: 26 Aug 2005

AB Recently we have shown that insulin fails to induce the phosphorylation of IRS-1 in the retina [Rajala et al. (2004) Biochemistry 43, 5637-5650], even though there is widespread expression of IRS-1 throughout the retina. These results suggest the expression of tissue-specific regulators in the retina. Yeast two-hybrid screening of a bovine retinal cDNA library with the cytoplasmic domain of retinal insulin receptor identified a novel member of the Grb7 gene family, Grb14. Phosphorylation prediction software indicated 6 out of 18 tyrosine residues were most likely to be phosphorylated. Out of six tyrosine phosphorylation sites, one of the tyrosine residues in Grb14 is present in a conserved sequence motif, FXNPXY. The NPXY motifs are recognized by proteins containing a domain known as phosphotyrosine-binding (PTB) or phosphotyrosine-interacting domain (PID). The biological function of the PTB domain is to drive recruitment of signaling adapters such as IRS-1 or Shc to NPXpY (pY stands for phosphotyrosine) on activated receptor tyrosine kinases. We have made a novel finding that the PTB domain of IRS-1 binds to the NPXY motif of Grb14 in a phosphorylation-independent manner. In addition, Grb14-IRS-1 complexes are detected in lysates prepared from retina tissues. We suggest that the Grb14 NPXY motif could be acting as a dominant negative for IRS-1 functions in the retina, and this hypothesis is consistent with the recent study that Grb14-deficient mice exhibit enhanced IRS-1 phosphorylation and activation of protein kinase B. This is the first

report describing the presence of the NPXY motif in Grb14 and binding of the PTB domain of IRS-1 in a phosphorylation-independent manner.

L38 ANSWER 9 OF 49 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:355085 HCAPLUS
DOCUMENT NUMBER: 140:369944
TITLE: Human tissue-specific housekeeping genes identified by expression profiling
INVENTOR(S): Aburatani, Hiroyuki; Yamamoto, Shogo
PATENT ASSIGNEE(S): NGK Insulators, Ltd., Japan
SOURCE: PCT Int. Appl., 372 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004035785	A1	20040429	WO 2002-JP10753		20021016
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2002344094	A1	20040504	AU 2002-344094		20021016
US 2004229233	A1	20041118	US 2003-684422		20031015
PRIORITY APPLN. INFO.:			US 2002-418614P	P	20021016
			WO 2002-JP10753	A	20021016

AB Housekeeping genes commonly expressed in 35 different human tissues, oligonucleotide probes and DNA microarrays containing them, are disclosed.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 10 OF 49 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:963345 SCISEARCH
THE GENUINE ARTICLE: 864TP
TITLE: Molecular basis of distinct interactions between Dok1 PTB domain and tyrosine-phosphorylated EGF receptor
AUTHOR: Zhang Y; Yan Z Y; Farooq A; Liu X J; Lu C L; Zhou M M (Reprint); He C
CORPORATE SOURCE: Mil Med Coll 2, Dept Neurobiol, Shanghai 200433, Peoples R China (Reprint); NYU, Mt Sinai Sch Med, Struct Biol Program, Dept Physiol & Biophys, New York, NY 10029 USA ming-ming.zhou@mssm.edu; chenghe@online.sh.cn
COUNTRY OF AUTHOR: Peoples R China; USA
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (29 OCT 2004) Vol. 343, No. 4, pp. 1147-1155.
ISSN: 0022-2836.
PUBLISHER: ACADEMIC PRESS LTD ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 30
ENTRY DATE: Entered STN: 25 Nov 2004
Last Updated on STN: 25 Nov 2004

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Phosphotyrosine binding (PTB) domains of the adaptor proteins Doks (downstream of tyrosine kinases) play an important role in regulating signal transduction of cell-surface receptors in cell growth, proliferation and differentiation; however, ligand specificity of the Dok PTB domains has until now remained elusive.. In this study, we have investigated the molecular basis of specific association between the Dok1 PTB domain and the tyrosine-phosphorylated EGFR. Using yeast two-hybrid and biochemical binding assays, we show that only the PTB domain from Dok1 but not Dok4 or Dok5 can selectively bind to two known tyrosine phosphorylation sites at Y1086 and Y1148 in EGFR. Our structure-based mutational analyses define the molecular determinants for the two distinct Dok1 PTB domain/EGFR interactions and provide the structural understanding of the specific interactions between EGFR and PTB domains in the divergent Dok homologues. (C) 2004 Elsevier Ltd. All rights reserved.

L38 ANSWER 11 OF 49 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2003127584 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12456510
TITLE: Felic (CIP4b), a novel binding partner with the Src kinase Lyn and Cdc42, localizes to the phagocytic cup.
AUTHOR: Dombrosky-Ferlan Patrice; Grishin Anatoly; Botelho Roberto J; Sampson Matthew; Wang Lin; Rudert William A; Grinstein Sergio; Corey Seth J
CORPORATE SOURCE: Department of Pediatrics, University of Pittsburgh, PA, USA.
SOURCE: Blood, (2003 Apr 1) Vol. 101, No. 7, pp. 2804-9. Electronic Publication: 2002-11-27. Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 19 Mar 2003 Last Updated on STN: 22 May 2003 Entered Medline: 21 May 2003

AB Through its Src homology 3 (SH3) and SH2 domains, the Src kinase Lyn interacts with a small number of phosphoproteins, such as Shc, Cbl, and Vav, which regulate cell cycle and the cytoskeleton. Using Lyn's Unique, SH3, and SH2 domains as bait in a yeast 2-hybrid screen, we isolated a novel gene product with features of a scaffolding protein. We named it Felic because it contains a domain homologous to the tyrosine kinase Fes and the cytoskeletal protein ezrin and forms a Lyn interaction with the GTPase Cdc42 (Felic). Felic was expressed in both hematopoietic and nonhematopoietic tissues. Because it represents an alternative splice product related to the Cdc42-interacting protein 4, CIP4, we also refer to Felic as CIP4b. Felic contains an SH3 recognition site RXPXXP and multiple tyrosine residues. In insulin or serum-stimulated HEK293 cells, Felic became tyrosine phosphorylated. Like CIP4, Felic associated with Cdc42 in its activated form only. Unlike CIP4, Felic does not possess a C-terminal SH3 domain. Coprecipitation studies show that Felic bound to Lyn or activated forms of Cdc42. Overexpression of Felic or CIP4 inhibited NIH 3T3 cell invasiveness in a Matrigel assay. Because Lyn and Cdc42 are involved in phagocytosis, we examined the distribution of Felic in RAW macrophages during particle ingestion. Felic was recruited more efficiently than CIP4 to the phagocytic cups. Altogether, these data suggest that CIP4/Felic constitute a novel family of cytoskeletal scaffolding proteins, integrating Src and Cdc42 pathways. The absence of an SH3 domain in Felic

provides a structural basis for functional differences.

L38 ANSWER 12 OF 49 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:425439 HCAPLUS
DOCUMENT NUMBER: 137:1571
TITLE: Shc-binding protein PAL (Protein expressed in Activated Lymphocytes) from mouse and human stimulating cell growth and division, cDNA encoding the same, and their uses
INVENTOR(S): McGlade, Jane; Schmandt, Rosemary
PATENT ASSIGNEE(S): Amgen Canada, Inc., Can.
SOURCE: U.S., 50 pp., Cont. of U. S. Ser. No. 83,587.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6399747	B1	20020604	US 1999-363708	19990729
US 6492138	B1	20021210	US 1998-83587	19980521
PRIORITY APPLN. INFO.:			US 1998-83587 A1	19980521

AB The present invention relates generally to the identification and isolation of a novel Shc-binding proteins, and to novel nucleic acid mols. encoding such proteins. In order to identify binding partners for p52 Shc protein a yeast -two hybrid system was used. A unique Shc binding protein designated PAL (Protein expressed in Activated Lymphocytes) have been isolated. PAL cDNA clones (mPAL for mouse and hPAL for human) have been isolated and characterized. The predicted amino acid sequence encoded by mPAL DNA contains 23 tyrosine residues, several of which are embedded in consensus binding motifs for SH2 domains. In addition, two highly acidic regions are encoded by the mPAL DNA. Comparison of both the nucleotide and protein sequences of mPAL with the GenBank databases revealed no significant homol. between mPAL and any previously identified proteins. Anti-mPAL antibodies were raised in rabbits. It was shown that interaction of mPAL protein with the Shc SH2 domain is not dependent on phosphorylation of mPAL. Expression of mPAL corelates with cellular proliferation. The invention is further directed to methods of producing PAL, to transgenic animal that produces PAL polypeptide, and to screening compns. for their ability to block cell division or proliferation.
REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 13 OF 49 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:257148 BIOSIS
DOCUMENT NUMBER: PREV200100257148
TITLE: IRIP (ImmunoReceptor-Interactive Protein) induces the activation of Lyn and Hck through SH2 and SH3 domains.
AUTHOR(S): Cen, Osman [Reprint author]; Stafford, Susan J. [Reprint author]; Alam, Rafeul [Reprint author]
CORPORATE SOURCE: University of Texas Medical Branch, 301 Univ Blvd, Galveston, TX, 77555-1083, USA
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1052. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 30 May 2001
Last Updated on STN: 19 Feb 2002

AB We have previously reported the cloning of IRIP as an IL-5Ralpha Interacting Protein using the yeast two-hybrid system. IL-5Ralpha is associated with Lyn tyrosine kinase and IRIP. In this study, we examined structural and functional interaction between IRIP and the Src-type kinases - Lyn and Hck. The interaction of IRIP with SH2 and SH3 domains of Lyn was studied in GST pull-down experiments. IRIP associated with the SH2 and SH3 domains of Lyn but not with the SH2 domain of Shc or the SH3 domain of Grb2. Next we assessed the association of Lyn with the peptides derived from IRIP. IRIP has both SH2 and SH3 binding motifs. A proline-rich (RxxPxxP) SH3 motif peptide from IRIP (PSH3) but not its mutant (PP-A) in which conserved Arginine and Proline residues were substituted with Alanine, pulled down Lyn from the cell lysate. Similarly both phosphorylated and non-phosphorylated SH2 motif peptides from IRIP (PSH2 and pPSH2, respectively) pulled down Lyn. Previous studies have shown that Src-type kinases can be activated through the interaction with SH2 and SH3 ligands. We investigated whether IRIP or IRIP-derived peptides induced Lyn activation. We showed that IRIP and its peptides - PSH3 and PSH2 but not PP-A induced Lyn autophosphorylation and its substrate (enolase) phosphorylation. IRIP and its peptides also induced activation of Hck, another member of Src family of tyrosine kinases but not that of Itk (an SH2 and SH2 domain-containing tyrosine kinase) or p38 MAP kinase. Our results indicate that IRIP specifically interacts with and activates Lyn and Hck. IRIP may represent a receptor-associated activator of Src-type kinases and play an important role in receptor signaling.

L38 ANSWER 14 OF 49 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001174627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11235915
TITLE: Human growth factor receptor bound 14 binds the activated insulin receptor and alters the insulin-stimulated tyrosine phosphorylation levels of multiple proteins.
AUTHOR: Hemming R; Agatep R; Badiani K; Wyant K; Arthur G; Gietz R D; Triggs-Raine B
CORPORATE SOURCE: Department of Biochemistry & Medical Genetics, University of Manitoba, Winnipeg, Canada.
SOURCE: Biochemistry and cell biology = Biochimie et biologie cellulaire, (2001) Vol. 79, No. 1, pp. 21-32.
Journal code: 8606068. ISSN: 0829-8211.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 18 Jun 2001
Last Updated on STN: 18 Jun 2001
Entered Medline: 14 Jun 2001

AB To identify proteins interacting in the insulin-signaling pathway that might define new pathways or regulate existing ones, we have employed the yeast two-hybrid system. In a two-hybrid screen of a human liver cDNA library, we identified the human growth factor receptor bound 14 (hGrb14) adaptor protein as a partner of the activated insulin receptor. Additional analysis of the insulin receptor--hGrb14 interaction in the yeast two-hybrid system revealed that the SH2 domain of hGrb14 was not the sole region involved in binding the activated insulin receptor. The insulin-stimulated interaction between hGrb14 and

the insulin receptor was also observed in different mammalian cultured cell lines. This association was detected at 1 min of insulin stimulation and was maximal at 10 nM and greater concentrations of insulin. Chinese hamster ovary cells stably expressing the insulin receptor (CHO-IR) and hGrb14 were used to examine the effects of hGrb14 overexpression on insulin-stimulated tyrosine phosphorylation of proteins; in general, increasing levels of hGrb14 expression resulted in a reduction in tyrosine phosphorylation. This decrease was demonstrated for the specific proteins src homology-containing and collagen-related protein (Shc), insulin receptor substrate-1 (IRS-1), and Downstream of tyrosine Kinase (Dok). The broad effects of hGrb14 overexpression on insulin-stimulated tyrosine phosphorylation suggest that it acts early in the insulin-signaling pathway.

L38 ANSWER 15 OF 49 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000309772 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10748052
TITLE: Direct binding of the signaling adapter protein Grb2 to the activation loop tyrosines on the nerve growth factor receptor tyrosine kinase, TrkA.
AUTHOR: MacDonald J I; Gryz E A; Kubu C J; Verdi J M; Meakin S O
CORPORATE SOURCE: John P. Robarts Research Institute, Neurodegeneration Group, 100 Perth Drive, London, Ontario N6A 5K8, Canada.
SOURCE: The Journal of biological chemistry, (2000 Jun 16) Vol. 275, No. 24, pp. 18225-33.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 28 Jul 2000
Last Updated on STN: 24 Aug 2000
Entered Medline: 20 Jul 2000
AB We demonstrate that the signaling adapter, Grb2, binds directly to the neurotrophin receptor tyrosine kinase, TrkA. Grb2 binding to TrkA is independent of Shc, FRS-2, phospholipase Cgamma-1, rAPS, and SH2B and is observed in in vitro binding assays, yeast two-hybrid assays, and in co-immunoprecipitation assays. Grb2 binding to TrkA is mediated by the central SH2 domain, requires a kinase-active TrkA, and is phosphotyrosine-dependent. By analyzing a series of rat TrkA mutants, we demonstrate that Grb2 binds to the carboxyl-terminal residue, Tyr(794), as well as to the activation loop tyrosines, Tyr(683) and Tyr(684). By using acidic amino acid substitutions of the activation loop tyrosines on TrkA, we can stimulate constitutive kinase activity and TrkA-Shc interactions but, importantly, abolish TrkA/Grb2 binding. Thus, in addition to providing the first evidence of direct Grb2 binding to the neurotrophin receptor, TrkA, these data provide the first direct evidence that the activation loop tyrosines of a receptor tyrosine kinase, in addition to their essential role in kinase activation, also serve a direct role in the recruitment of intracellular signaling molecules.

L38 ANSWER 16 OF 49 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2000200449 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10734103
TITLE: Identification and characterization of a dimerization domain in CED-6, an adapter protein involved in engulfment of apoptotic cells.
AUTHOR: Su H P; Brugnera E; Van Criekinge W; Smits E; Hengartner M; Bogaert T; Ravichandran K S
CORPORATE SOURCE: Beirne Carter Center for Immunology Research and the Department of Microbiology, University of Virginia,

Charlottesville, Virginia 22908, USA.
SOURCE: The Journal of biological chemistry, (2000 Mar 31) Vol. 275, No. 13, pp. 9542-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 12 May 2000
Last Updated on STN: 12 May 2000
Entered Medline: 4 May 2000

AB Phagocytosis of apoptotic cells is a key step in the completion of programmed cell death that occurs throughout life in multicellular organisms. The molecular events involved in clearance of apoptotic cells are just beginning to be elucidated. Recently, CED-6, an adapter protein involved in engulfment has been cloned in Caenorhabditis elegans and in humans. CED-6 is composed of a phosphotyrosine-binding (PTB) domain and a proline-rich C-terminal domain with no apparent catalytic domain. Since PTB domains, originally identified in Shc, mediate intracellular signaling downstream of cell surface receptors, CED-6 has also been proposed to mediate intracellular signals leading to engulfment. In this report, we demonstrate that CED-6 dimerizes through a leucine zipper domain that is immediately adjacent to the PTB domain. Several lines of evidence based on co-immunoprecipitation studies, yeast two-hybrid assays, and gel filtration studies suggest that CED-6 exists as a dimer in vivo. Through mutational analyses, we show that the leucine zipper is necessary and sufficient for CED-6 dimerization and that this dimerization is conserved among C. elegans, rodent, and human CED-6 proteins. We propose that dimerization may have unique implications for ligand binding via CED-6 and its function during the phagocytosis of apoptotic cells.

L38 ANSWER 17 OF 49 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2000114365 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10650943
TITLE: Potential involvement of FRS2 in insulin signaling.
AUTHOR: Delahaye L; Rocchi S; Van Obberghen E
CORPORATE SOURCE: INSERM, U-145 and IFR 50, Nice, France.. delahaye@unice.fr
SOURCE: Endocrinology, (2000 Feb) Vol. 141, No. 2, pp. 621-8.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 18 Feb 2000
Last Updated on STN: 18 Feb 2000
Entered Medline: 10 Feb 2000

AB Shp-2 is implicated in several tyrosine kinase receptor signaling pathways. This phosphotyrosine phosphatase is composed of a catalytic domain in its C-terminus and two SH2 domains in its N-terminus. Shp-2 becomes activated upon binding through one or both SH2 domains to tyrosine phosphorylated molecules such as Shc or insulin receptor substrates. We were interested in finding a new molecule(s), tyrosine phosphorylated by the insulin receptor (IR), that could interact with Shp-2. To do so, we screened a human placenta complementary DNA (cDNA) library with the SH2 domain-containing part of Shp-2 using a modified yeast two-hybrid system. In this system we induce or repress the expression of a constitutive active IR beta-subunit. When expressed, IR phosphorylates proteins produced from the library that can then associate with Shp-2.

Using this approach, we isolated FRS2 as a potential target for tyrosine phosphorylation by the IR. After cloning the entire cDNA, we found that 1) in the yeast two-hybrid system, FRS2 interacts with Shp-2 in a fashion dependent on the presence of the IR; and 2) in the PC12/IR cell-line, insulin leads to an increase in FRS2 association with the phosphatase. We next wanted to determine whether FRS2 could be a direct substrate for IR. In an in vitro kinase assay we found that wheat-germ agglutinin-purified IR phosphorylates glutathione-S-transferase-FRS2 fusion protein. Finally, in intact cells we show that insulin stimulates tyrosine phosphorylation of endogenous FRS2. In summary, by screening a two-hybrid cDNA library, we have isolated FRS2 as a possible substrate for IR. We found that IR can directly phosphorylate FRS2. Moreover, in intact cells insulin stimulates tyrosine phosphorylation of FRS2 and its subsequent association with Shp-2. Taken together these results suggest that FRS2 could participate in insulin signaling by recruiting Shp-2 and, hence, could function as a docking molecule similar to insulin receptor substrate proteins.

L38 ANSWER 18 OF 49 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2001132966 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10749680
TITLE: The Shc-related adaptor protein, Sck, forms a complex with the vascular-endothelial-growth-factor receptor KDR in transfected cells.
AUTHOR: Warner A J; Lopez-Dee J; Knight E L; Feramisco J R; Prigent S A
CORPORATE SOURCE: Department of Biochemistry, University of Leicester, Leicester LE1 7RH, UK.
SOURCE: The Biochemical journal, (2000 Apr 15) Vol. 347, No. Pt 2, pp. 501-9.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 4 Apr 2001
Last Updated on STN: 4 Apr 2001
Entered Medline: 1 Mar 2001

AB Despite much progress in recent years, the precise signalling events triggered by the vascular-endothelial-growth-factor (VEGF) receptors, fms-like tyrosine kinase (Flt1) and kinase insert domain-containing receptor (KDR), are incompletely defined. Results obtained when Flt1 and KDR are individually expressed in fibroblasts or porcine aortic endothelial cells have not been entirely consistent with those observed in other endothelial cells expressing both receptors endogenously. It has also been difficult to demonstrate VEGF-induced phosphorylation of Flt1, which has led to speculation that KDR may be the more important receptor for the mitogenic action of VEGF on endothelial cells. In an attempt to identify physiologically important effectors which bind to KDR, we have screened a yeast two-hybrid mouse embryo library with the cytoplasmic domain of KDR. Here we describe the identification of the adaptor protein, Shc-like protein (Sck), as a binding partner for KDR. We demonstrate that this interaction requires phosphorylation of KDR, and identify the binding site for the Src-homology 2 (SH2) domain as tyrosine-1175 of KDR. We have also shown that the SH2 domain of Sck, but not that of Src-homology collagen protein (Shc), can precipitate phosphorylated KDR from VEGF-stimulated porcine aortic endothelial cells expressing KDR, and that an N-terminally truncated Sck protein can associate with KDR, in a phosphorylation-dependent fashion, when co-expressed in human embryonic kidney 293 cells. Furthermore, we demonstrate that in the two-hybrid assay, both Shc and Sck

SH2 domains can associate with the related receptor Flt1.

L38 ANSWER 19 OF 49 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:811448 HCAPLUS
DOCUMENT NUMBER: 132:32921
TITLE: Preparation and usage of fusion proteins as bioluminescence resonance energy transfer (BRET) systems
INVENTOR(S): Joly, Erik; Johnson, Carl H.; Piston, David W.
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966324	A2	19991223	WO 1999-CA561	19990616
WO 9966324	A3	20000406		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335305	A1	19991223	CA 1999-2335305	19990616
CA 2335305	C	20060523		
CA 2541920	A1	19991223	CA 1999-2541920	19990616
AU 9942542	A	20000105	AU 1999-42542	19990616
EP 1088233	A2	20010404	EP 1999-957096	19990616
EP 1088233	B1	20051109		
R: CH, DE, FR, GB, LI, NL, SE, IE				

PRIORITY APPLN. INFO.:	US 1998-89623P	P	19980616
	CA 1999-2335305	A3	19990616
	WO 1999-CA561	W	19990616

AB This invention provides bioluminescence resonance energy transfer (BRET) system that comprises four parts: (1) a bioluminescent protein that has luciferase activity; (2) an acceptor fluorophore that can accept the energy from the bioluminescent protein when they are associated, in the presence of the appropriate substrate; (3) a modulator that influences the proximity or the orientation of the bioluminescent protein and the fluorophore, and (4) an appropriate substrate to activate the luciferase activity of the bioluminescent protein. The components of this system interact to influence the spatial relationship between the bioluminescent protein and the fluorophore, that is demonstrated by the light emission from the system. The modulator can be a single entity, covalently attached to both the bioluminescent protein and the fluorophore, it can be two sep. entities, each linked covalently to either the bioluminescent protein or the fluorophore, or an alternative configuration that falls within the scope of the invention. This system can be used in both in vivo or in vitro assays to detect mol. changes in a wide variety of applications, and is amenable to automation. In particular, it is useful for assaying protein interactions, enzyme activities and the concentration of analytes or signaling mols. in cells or in solution

L38 ANSWER 20 OF 49 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:930671 SCISEARCH
THE GENUINE ARTICLE: 260XW

TITLE: Interaction of c-Jun amino-terminal kinase interacting protein-1 with p190 rhoGEF and its localization in differentiated neurons

AUTHOR: Meyer D; Liu A; Margolis B (Reprint)

CORPORATE SOURCE: Univ Michigan, Med Ctr, Howard Hughes Med Inst, Sch Med, 4570 MSRB 2, Box 0650, 1150 W Med Ctr Dr, Ann Arbor, MI 48109 USA (Reprint); Univ Michigan, Med Ctr, Howard Hughes Med Inst, Sch Med, Ann Arbor, MI 48109 USA; Univ Michigan, Sch Med, Dept Biol Chem, Ann Arbor, MI 48109 USA; Univ Michigan, Sch Med, Dept Internal Med, Ann Arbor, MI 48109 USA

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (3 DEC 1999) Vol. 274, No. 49, pp. 35113-35118.
ISSN: 0021-9258.

PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 37

ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB c-Jun amino-terminal kinase (JNK) interacting protein-1 (JIP-1) was originally identified as a cytoplasmic inhibitor of JNK, More recently, JIP-1 was proposed to function as a scaffold protein by complexing specific components of the JNK signaling pathway, namely JNK, mitogen-activated protein kinase kinase 7, and mixed lineage kinase 3, We have identified the human homologue of JIP-1 that contains a phosphotyrosine binding (PTB) domain in addition to a JNK binding domain and an Src homology 3 domain. To identify binding targets for the hJIP-1 PTB domain, a mouse embryo cDNA library was screened using the yeast two-hybrid system. One clone encoded a 191-amino acid region of the neuronal protein rhoGEF, an exchange factor for rhoA, Overexpression of rhoGEF promotes cytoskeletal rearrangement and cell rounding in NIE-115 neuronal cells. The interaction of JIP-1 with rhoGEF was confirmed by coimmunoprecipitation of these proteins from lysates of transiently transfected HEK 293 cells. Using glutathione S-transferase rhoGEF fusion proteins containing deletion or point mutations, we identified a putative PTB binding site within rhoGEF, This binding site does not contain tyrosine, indicating that the JIP PTB domain, like that of X11 alpha and Numb, binds independently of phosphotyrosine, Several forms of endogenous JIP-1 protein can be detected in neuronal cell lines. Indirect immunofluorescence analysis localized endogenous JIP-1 to the tip of the neurites in differentiated NIE-115 and PC12 cells. The interaction of JIP-1 with rhoGEF and its subcellular localization suggests that JIP-1 may function to specifically localize a signaling complex in neuronal cells.

L38 ANSWER 21 OF 49 MEDLINE on STN DUPLICATE 11

ACCESSION NUMBER: 1999262689 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10329736

TITLE: Interaction of insulin receptor substrate 3 with insulin receptor, insulin receptor-related receptor, insulin-like growth factor-1 receptor, and downstream signaling proteins.

AUTHOR: Xu P; Jacobs A R; Taylor S I

CORPORATE SOURCE: Diabetes Branch, NIDDK, National Institutes of Health, Bethesda, Maryland 20892, USA.

SOURCE: The Journal of biological chemistry, (1999 May 21) Vol. 274, No. 21, pp. 15262-70.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 27 Jul 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 9 Jul 1999

AB Insulin receptor substrates (IRS) mediate biological actions of insulin, growth factors, and cytokines. All four mammalian IRS proteins contain pleckstrin homology (PH) and phosphotyrosine binding (PTB) domains at their N termini. However, the molecules diverge in their C-terminal sequences. IRS3 is considerably shorter than IRS1, IRS2, and IRS4, and is predicted to interact with a distinct group of downstream signaling molecules. In the present study, we investigated interactions of IRS3 with various signaling molecules. The PTB domain of mIRS3 is necessary and sufficient for binding to the juxtamembrane NPXpY motif of the insulin receptor in the yeast two-hybrid system. This interaction is stronger if the PH domain or the C-terminal phosphorylation domain is retained in the construct. As determined in a modified yeast two-hybrid system, mIRS3 bound strongly to the p85 subunit of phosphatidylinositol 3-kinase. Although high affinity interaction required the presence of at least two of the four YXXM motifs in mIRS3, there was not a requirement for specific YXXM motifs. mIRS3 also bound to SHP2, Grb2, Nck, and Shc, but less strongly than to p85. Studies in COS-7 cells demonstrated that deletion of either the PH or the PTB domain abolished insulin-stimulated phosphorylation of mIRS3. Insulin stimulation promoted the association of mIRS3 with p85, SHP2, Nck, and Shc. Despite weak association between mIRS3 and Grb2, this interaction was not increased by insulin, and may not be mediated by the SH2 domain of Grb2. Thus, in contrast to other IRS proteins, mIRS3 appears to have greater specificity for activation of the phosphatidylinositol 3-kinase pathway rather than the Grb2/Ras pathway.

L38 ANSWER 22 OF 49 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 1999389880 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10460257
TITLE: Disabled-1 binds to the cytoplasmic domain of amyloid precursor-like protein 1.
AUTHOR: Homayouni R; Rice D S; Sheldon M; Curran T
CORPORATE SOURCE: Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
CONTRACT NUMBER: 5T32 CA09346 (NCI)
P30 CA21765 (NCI)
R01-NS36558 (NINDS)
SOURCE: The Journal of neuroscience : the official journal of the Society for Neuroscience, (1999 Sep 1) Vol. 19, No. 17, pp. 7507-15.
Journal code: 8102140. E-ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 5 Oct 1999
Last Updated on STN: 21 May 2001
Entered Medline: 23 Sep 1999

AB Disruption of the disabled-1 gene (Dab1) results in aberrant migration of neurons during development and disorganization of laminar structures throughout the brain. Dab1 is thought to function as an adapter molecule in signal transduction processes. It contains a protein-interaction (PI)

domain similar to the phosphotyrosine-binding domain of the Shc oncoprotein, it is phosphorylated by the Src protein tyrosine kinase, and it binds to SH2 domains in a phosphotyrosine-dependent manner. To investigate the function of Dab1, we searched for binding proteins using the yeast two-hybrid system. We found that the PI domain of Dab1 interacts with the amyloid precursor-like protein 1 (APLP1). The association of Dab1 with APLP1 was confirmed in biochemical assays, and the site of interaction was localized to a cytoplasmic region of APLP1 containing the amino acid sequence motif Asn-Pro-x-Tyr (NPxY). NPxY motifs are involved in clathrin-mediated endocytosis, and they have been shown to bind to PI domains present in several proteins. This region of APLP1 is conserved among all members of the amyloid precursor family of proteins. Indeed, we found that Dab1 also interacts with amyloid precursor protein (APP) and APLP2 in biochemical association experiments. In transiently transfected cells, Dab1 and APLP1 colocalized in membrane ruffles and vesicular structures. Cotransfection assays in cultured cells indicated that APP family members increased serine phosphorylation of Dab1. Dab1 and APLP1 are expressed in similar cell populations in developing and adult brain tissue. These results suggest that Dab1 may function, at least in part, through association with APLP1 in the brain.

L38 ANSWER 23 OF 49 MEDLINE on STN DUPLICATE 13

ACCESSION NUMBER: 1999184145 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10086341
TITLE: Cloning and characterization of mPAL, a novel Shc SH2 domain-binding protein expressed in proliferating cells.
AUTHOR: Schmandt R; Liu S K; McGlade C J
CORPORATE SOURCE: Ontario Cancer Institute, University of Toronto, Canada.
SOURCE: Oncogene, (1999 Mar 11) Vol. 18, No. 10, pp. 1867-79. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF017152
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 26 Apr 1999
Last Updated on STN: 26 Apr 1999
Entered Medline: 13 Apr 1999

AB Shc adaptor proteins play a role in linking activated cell surface receptors to the Ras signaling pathway in response to receptor mediated tyrosine kinase activation. While the function of Shc in the activation of the Ras pathway via binding to Grb2 has been well characterized, it is becoming increasingly apparent that Shc participates in additional signaling pathways through interactions with other cytoplasmic proteins. Using the yeast two-hybrid system, we have identified a unique Shc binding protein designated PAL (Protein expressed in Activated Lymphocytes) with no similarity to other known proteins. mPAL binds specifically to the Shc SH2 domain and unlike previously described Shc SH2 domain-protein interactions, the association of mPAL and Shc is phosphotyrosine-independent. Both mPAL RNA and protein expression are restricted to tissues containing actively dividing cells and proliferating cells in culture. mPAL expression is induced upon growth factor stimulation and is down-regulated upon growth inhibition. This pattern, and timing of mPAL expression and its association with the Shc adaptor molecule suggests a role for this protein in signaling pathways governing cell cycle progression.

L38 ANSWER 24 OF 49 MEDLINE on STN DUPLICATE 14

ACCESSION NUMBER: 1999381784 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10453981
TITLE: Differential regulation of signaling pathways for insulin and insulin-like growth factor I.
AUTHOR: Lopaczynski W
CORPORATE SOURCE: Endocrinology Section, Metabolism Branch, National Cancer Institute, Bethesda, Maryland 20892-1374, USA.. WLX@CU.NIH.GOV
SOURCE: Acta biochimica Polonica, (1999) Vol. 46, No. 1, pp. 51-60. Ref: 52
Journal code: 14520300R. ISSN: 0001-527X.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 12 Oct 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 30 Sep 1999

AB The insulin receptor (IR) and the insulin-like growth factor receptor I (IGF-IR) have different functions in cell growth, apoptosis, differentation, and transformation. Although some of these differences may be explained by the relative level of receptor expression and receptor structure (alpha and beta subunits), they may also be attributed to differences in intracellular signals generated by insulin and IGF-I. The presence of hybrid receptors (IR alphabeta subunits and IGF-IR alphabeta subunits) making up the heterotetramers has added a new dimension to our understanding of the functional roles of these receptors. However, to date the results of efforts to understand the differences between these two closely related receptors have indicated mostly similarities. For example, both receptors utilize IRS-1/IRS-2 and Shc as immediate downstream adaptors, leading to activation of the Ras, Raf, ERK kinases and PI-3 kinase pathways. We have used the yeast two hybrid system to identify proteins which bind to the activated IGF-IR but not to the IR. The cytoplasmic domain of the IGF-IR was used to screen a human fetal brain library and two isoforms of the 14-3-3 family were identified. 14-3-3 proteins are a highly conserved family of proteins which have recently been shown to interact with other components of the mitogenic and apoptotic signaling pathways, including Raf, BAD, Bcr/Bcr-Abl, middle-T antigen, Ksr, PKC, PI-3 kinase, ASK1 kinase, and cdc25C phosphatase. We also identified human Grb10, an adaptor protein with SH2 domain associated with the IGF-IR beta subunit. Smith's laboratory showed that Grb10 preferentially binds to the IR in intact cells. Using the interaction trap screen (active cytoplasmic domain of the IGF-IR) 55PIK and SOCS-2 proteins were also identified. However, 55PIK and SOCS-2 also interact with the IR in the yeast two hybrid system. These studies raise the possibility that 14-3-3 and Grb10 may play a role in insulin and IGF-I signal transduction and may underlie the observed differences.

L38 ANSWER 25 OF 49 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:251265 HCAPLUS
DOCUMENT NUMBER: 128:305398
TITLE: Fusion proteins containing multiple domains binding to a target protein and their investigative and therapeutic uses
INVENTOR(S): Cowburn, David; Zheng, Jie; Barany, George; Xu, Qinhong
PATENT ASSIGNEE(S): Rockefeller University, USA; Regents of the University of Minnesota
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9816638	A1	19980423	WO 1996-US16495	19961016
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9674324	A	19980511	AU 1996-74324	19961016
PRIORITY APPLN. INFO.:			WO 1996-US16495 W	19961016

AB Consolidated ligand proteins containing peptides that bind to at least two domains of a target protein are described. These consolidated ligands have increased affinity for the target protein over ligands directed to a single domain. Particularly preferred ligands include those directed to the Src homol. 2 and 3 (SH2, SH3) domains of eukaryotic protein tyrosine kinases involved in complex regulation of growth and differentiation. Ligands of this kind of design may be widely useful as reagents in the investigation of SH interactions, and as leads for design of therapeutic agents.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 26 OF 49 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 1998204916 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9535908
TITLE: The mammalian numb phosphotyrosine-binding domain. Characterization of binding specificity and identification of a novel PDZ domain-containing numb binding protein, LNX.
AUTHOR: Dho S E; Jacob S; Wolting C D; French M B; Rohrschneider L R; McGlade C J
CORPORATE SOURCE: AMGEN Institute, Ontario Cancer Institute, Department of Medical Biophysics, University of Toronto, Toronto, Canada M5G 2C1.
SOURCE: The Journal of biological chemistry, (1998 Apr 10) Vol. 273, No. 15, pp. 9179-87.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF034745; GENBANK-AF034746
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 20 May 1998
Last Updated on STN: 20 May 1998
Entered Medline: 14 May 1998

AB Numb is a phosphotyrosine-binding (PTB) domain-containing protein implicated in the control of cell fate decisions during development. A modified two-hybrid screen in yeast was used to identify Numb PTB domain-interacting proteins important for Numb function. Here we report the identification of a novel protein, LNX, which interacts specifically with the Numb PTB domain. Two differentially expressed LNX messages encode overlapping proteins with predicted molecular masses of 80 kDa (LNX) and 70 kDa (LNX-b). LNX and LNX-b contain unique amino-terminal sequences and share four PDZ domains. The unique amino-terminal region of LNX includes a RING finger domain. The Numb PTB domain binding region of LNX was mapped to the sequence motif LDNPAY, found in both protein isoforms. Mutational analysis of LNX and peptide competition experiments showed that phosphorylation of the tyrosine residue within this motif was not required for binding to the Numb PTB domain.

Finally, we also provide evidence that tyrosine phosphorylation of the LDNPAY sequence motif in LNX could generate a binding site for the phosphorylation-dependent binding of other PTB domain-containing proteins such as SHC. We speculate that LNX may be important for clustering PTB-containing proteins with functionally related transmembrane proteins in specific membrane compartments.

L38 ANSWER 27 OF 49 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 1998414809 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9742401
TITLE: Src-like adaptor protein (Slap) is a negative regulator of mitogenesis.
AUTHOR: Roche S; Alonso G; Kazlauskas A; Dixit V M; Courtneidge S A; Pandey A
CORPORATE SOURCE: CNRS EP612, Faculte de Pharmacie, Montpellier, France.
CONTRACT NUMBER: DK 54386 (NIDDK)
SOURCE: Current biology : CB, (1998 Aug 27) Vol. 8, No. 17, pp. 975-8.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 6 Jan 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 18 Nov 1998

AB The Src-like adaptor protein (Slap) is a recently identified adaptor protein containing Src homology 3 (SH3) and SH2 domains. Slap is found in a wide range of cell types and was shown to interact with the Eck receptor tyrosine kinase in a yeast two-hybrid interaction screen [1]. Here, we found that Slap is expressed in NIH3T3 cells and could associate with the activated platelet-derived growth factor (PDGF) receptor. Using mutated versions of the PDGF receptor and phosphopeptide competition experiments, we determined that Slap has the highest affinity for the Src-binding site of the PDGF receptor. Our inability to produce cell lines that stably expressed Slap suggested that Slap inhibited cell growth. We further investigated this issue by transiently expressing Slap by microinjection. Overexpression of Slap by this method inhibited DNA synthesis induced by PDGF and serum, whereas overexpression of the adaptor proteins Grb2 and Shc did not. Finally, microinjection of a Slap antibody into NIH3T3 cells that had been stimulated with suboptimal doses of growth factors potentiated the effects of the growth factors. These data suggest that, unlike other adaptor proteins, Slap is a negative regulator of signalling initiated by growth factors.

L38 ANSWER 28 OF 49 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 1998337468 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9674711
TITLE: Tyrosine-614, the major autophosphorylation site of the receptor tyrosine kinase HEK2, functions as multi-docking site for SH2-domain mediated interactions.
AUTHOR: Hock B; Bohme B; Karn T; Feller S; Rubsamen-Waigmann H; Strebhardt K
CORPORATE SOURCE: Chemotherapeutisches Forschungsinstitut, Georg-Speyer-Haus, Frankfurt, Germany.
SOURCE: Oncogene, (1998 Jul 16) Vol. 17, No. 2, pp. 255-60.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 17 Aug 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 6 Aug 1998

AB HEK2 belongs to the family of EPH-related receptor tyrosine kinases (RTK) which are involved in axonal pathfinding and the formation of the embryonic body plan. The knowledge about intracellular pathways of signal transduction mediated by EPH-related receptors is still limited. Many of the known key players of cellular signalling contain Src homology 2 (SH2) domains, which recognize phosphotyrosine motifs in RTKs. Thus, we examined the interactions of various SH2-containing molecules like PLC-gamma1, rasGAP, p85 subunit of PI3-kinase, Src, Fyn, Crk, Nck, Grb2 and Shc with HEK2 using in vitro binding assays, immunoprecipitations and yeast Two-Hybrid assays. We found that rasGAP, Crk and Fyn bind in a SH2-dependent manner to autophosphorylated HEK2. rasGAP, which contains two SH2 - and one SH3-domain, was shown to associate with its N-terminal SH2-domain to HEK2. Furthermore, we demonstrated that a single amino acid substitution (Y614F) clearly reduces the phosphotyrosine content of HEK2 and abrogates its ability to bind rasGAP, Crk and Fyn indicating that this residue functions as major phosphorylation and multi-docking site. The conservation of this predicted binding site among various EPH-related RTKs provides evidence that Fyn, Crk and rasGAP are key players in signal transduction of at least a subset of these receptors.

L38 ANSWER 29 OF 49 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 1999009225 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9790910
TITLE: Sck interacts with KDR and Flt-1 via its SH2 domain.
AUTHOR: Igarashi K; Shigeta K; Isohara T; Yamano T; Uno I
CORPORATE SOURCE: Advanced Technology Research Laboratories, Nippon Steel Corporation, 3-35-1 Ida, Kawasaki, Nakahara-Ku, 211-0035, Japan.. igarashi@lab1.nsc.co.jp
SOURCE: Biochemical and biophysical research communications, (1998 Oct 9) Vol. 251, No. 1, pp. 77-82.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 6 Jan 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Nov 1998

AB Vascular endothelial growth factor (VEGF) is one of the major angiogenesis regulators. It binds to its tyrosine kinase receptors, KDR and Flt-1. However, little is known about their downstream signal transduction properties. We screened human brain cDNA library using the yeast two-hybrid system with the KDR cytoplasmic region as bait to find KDR binding proteins. After 6.2 x 10(6) clones were screened, we identified Sck, one of the Shc homologues, as a KDR binding protein. Sck also binds to Flt-1 and their binding is dependent on the kinase activities of KDR and Flt-1. Extensive site-directed mutagenesis of KDR revealed that Y1175 of KDR is a major binding site for Sck. As Sck contains the SH2 domain and PTB domain, we tested whether they bind to KDR and Flt-1. The SH2 domain of Sck binds to both of them. Deletion of the SH2 domain from Sck resulted in the complete loss of binding. On the other hand, the PTB

domain of Sck does not bind to KDR and Flt-1. These results indicate that Sck binds to KDR and Flt-1 via its SH2 domain and might play an important role in VEGF signal transduction. Copyright 1998 Academic Press.

L38 ANSWER 30 OF 49 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:3936 SCISEARCH
THE GENUINE ARTICLE: 150HA
TITLE: Insulin-like growth factor-I receptor signal transduction: at the interface between physiology and cell biology
AUTHOR: Butler A A; Yakar S; Gewolb I H; Karas M; Okubo Y; LeRoith D (Reprint)
CORPORATE SOURCE: NIDDKD, Sect Mol & Cellular Physiol, Diabet Branch, NIH, Room 8S 235A, Bldg 10, 10 Ctr Dr, MSC 1770, Bethesda, MD 20892 USA (Reprint); NIDDKD, Sect Mol & Cellular Physiol, Diabet Branch, NIH, Bethesda, MD 20892 USA
COUNTRY OF AUTHOR: USA
SOURCE: COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY B-BIOCHEMISTRY & MOLECULAR BIOLOGY, (SEP 1998) Vol. 121, No. 1, pp. 19-26. ISSN: 1096-4959.
PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 59
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The insulin-like growth factor-I receptor (IGF-IR) mediates the biological actions of IGF-I and IGF-II. The IGFs play a critical role in promoting development, stimulating growth and organogenesis via mitogenic, antiapoptotic and chemotactic activity. Recent research has focused on the events that occur intracellularly upon receptor activation. Several pathways have been shown to be important. The insulin-receptor substrate (IRS), SHC, GRB2, CRKII and CRKL adaptor proteins have all been implicated in transmitting signals to the nucleus of the cell. This review outlines some of the signalling pathways believed to be important in converting IGF-IR activation into changes in cell behavior and metabolism. (C) 1998 Published by Elsevier Science inc.

L38 ANSWER 31 OF 49 NTIS COPYRIGHT 2007 NTIS on STN

ACCESSION NUMBER: 1998(19):00378
NTIS ORDER NUMBER: AD-A340 952/1/XAB
TITLE: Ret Receptor: Functional Consequences of Oncogenic Rearrangements. Annual rept. 15 Sep 94-14 Sep 97.
AUTHOR: Taylor, S. S.
CORPORATE SOURCE: California Univ., San Diego, La Jolla. (005436000 072380)
NUMBER OF REPORT: AD-A340 952/1/XAB
27p; Oct 1997
NUMBER OF CONTRACT: DAMD17-94-J-4120
CONTROLLED TERM: Report
COUNTRY: United States
LANGUAGE: English
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NTIS Prices: PC A03/MF A01
OTHER SOURCE: GRA&I9815

AB Ret/ptc2 is a soluble, constitutively active oncogenic protein whose gene was cloned from human papillary thyroid carcinomas. Ret/ptc2 is a chimeric protein resulting from a reciprocal chromosomal rearrangement translocation event between the cAMP-dependent protein kinase regulatory subunit type Ialpha (RIalpha) and the tyrosine kinase domain of the Ret receptor. Earlier microinjection studies showed the RIalpha dimerization domain is critical for eliciting a mitogenic response in mouse 1OT 1/2 fibroblasts. By combining results obtained from microinjection studies of Ret/ptc2 point mutants and mapping proteins identified from a yeast two-hybrid screen to a computer generated model of the Ret/ptc2 kinase core, we have previously identified specific tyrosine residues to which the SH2 domains of Grb10 and PLCgamma, the second C-terminal LIM domain of Enigma, and the PTB domain of Shc interact. From our recent characterization of the Enigma-Shc dual association with Ret/ptc2 in mouse 1OT 1/2 fibroblasts, we propose the mitogenic response elicited by Ret/ptc2 requires Enigma for proper cellular localization and utilizes the Ras pathway via the recruitment and phosphorylation of Shc. In addition to these studies, we have overexpressed and purified His6-Ret/ptc2 from the methylotrophic yeast, Pichia pastoris, to initiate extensive in vitro biochemical and biophysical characterization.

L38 ANSWER 32 OF 49 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1998:4573 BIOSIS
DOCUMENT NUMBER: PREV199800004573
TITLE: SH2/SH3 adaptor proteins can link tyrosine kinases to a Ste20-related protein kinase, HPK1.
AUTHOR(S): Anafi, Mordechai; Keifer, Friedemann; Gish, Gerald D.; Mbamalu, Geraldine; Iscove, Norman N.; Pawson, Tony [Reprint author]
CORPORATE SOURCE: Programme Mol. Biol. Cancer, Samuel Lunenfeld Res. Isnt., Mount Sinai Hosp., 600 University Ave., Toronto, ON M5G 1X5, Canada
SOURCE: Journal of Biological Chemistry, (Oct. 31, 1997) Vol. 272, No. 44, pp. 27804-27811. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Dec 1997
Last Updated on STN: 23 Dec 1997

AB Ste20-related protein kinases have been implicated as regulating a range of cellular responses, including stress-activated protein kinase pathways and the control of cytoskeletal architecture. An important issue involves the identities of the upstream signals and regulators that might control the biological functions of mammalian Ste20-related protein kinases. HPK1 is a protein-serine/threonine kinase that possesses a Ste20-like kinase domain, and in transfected cells activates a protein kinase pathway leading to the stress-activated protein kinase SAPK/JNK. Here we have investigated candidate upstream regulators that might interact with HPK1. HPK1 possesses an N-terminal catalytic domain and an extended C-terminal tail with four proline-rich motifs. The SH3 domains of Grb2 bound in vitro to specific proline-rich motifs in the HPK1 tail and functioned synergistically to direct the stable binding of Grb2 to HPK1 in transfected Cos1 cells. Epidermal growth factor (EGF) stimulation did not affect the binding of Grb2 to HPK1 but induced recruitment of the Grb2-HPK1 complex to the autophosphorylated EGF receptor and to the Shc docking protein. Several activated receptor and cytoplasmic tyrosine kinases, including the EGF receptor, stimulated the tyrosine phosphorylation of the HPK1 serine/threonine kinase. These results suggest that HPK1, a mammalian Ste20-related protein-serine/threonine kinase, can potentially associate with protein-tyrosine kinases through interactions mediated by SH2

/SH3 adaptors such as Grb2. Such interaction may provide a possible mechanism for cross-talk between distinct biochemical pathways following the activation of tyrosine kinases.

L38 ANSWER 33 OF 49 MEDLINE on STN
ACCESSION NUMBER: 97298039 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9153187
TITLE: Interaction of the adaptor protein Shc and the adhesion molecule cadherin.
AUTHOR: Xu Y; Guo D F; Davidson M; Inagami T; Carpenter G
CORPORATE SOURCE: Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, USA.
CONTRACT NUMBER: CA24071 (NCI)
CA68485 (NCI)
HL35323 (NHLBI)
+
SOURCE: The Journal of biological chemistry, (1997 May 23) Vol. 272, No. 21, pp. 13463-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 16 Jul 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 2 Jul 1997

AB In mitogenic signaling pathways, Shc participates in the growth factor activation of Ras by interacting with activated receptors and/or the Grb-2.Sos complex. Using several experimental approaches we demonstrate that Shc, through its SH2 domain, forms a complex with the cytoplasmic domain of cadherin, a transmembrane protein involved in the Ca2+-dependent regulation of cell-cell adhesion. This interaction is demonstrated in a yeast two-hybrid assay, by co-precipitation from mammalian cells, and by direct biochemical analysis in vitro. The Shc-cadherin association is phosphotyrosine-dependent and is abrogated by addition of epidermal growth factor to A-431 cells maintained in Ca2+-free medium, a condition that promotes changes in cell shape. Shc may therefore participate in the control of cell-cell adhesion as well as mitogenic signaling through Ras.

L38 ANSWER 34 OF 49 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 1998038806 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9372969
TITLE: Adenovirus-mediated overexpression of IRS-1 interacting domains abolishes insulin-stimulated mitogenesis without affecting glucose transport in 3T3-L1 adipocytes.
AUTHOR: Sharma P M; Egawa K; Gustafson T A; Martin J L; Olefsky J M
CORPORATE SOURCE: Department of Medicine, University of California, San Diego, La Jolla 92093, USA.
CONTRACT NUMBER: R01 DK 36651 (NIDDK)
T32 DK 07202 (NIDDK)
SOURCE: Molecular and cellular biology, (1997 Dec) Vol. 17, No. 12, pp. 7386-97.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712

ENTRY DATE: Entered STN: 9 Jan 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 16 Dec 1997

AB Activated insulin receptor (IR) interacts with its substrates, IRS-1, IRS-2, and Shc via the NPXY motif centered at Y960. This interaction is important for IRS-1 phosphorylation. Studies using the yeast two-hybrid system and sequence identity analysis between IRS-1 and IRS-2 have identified two putative elements, the PTB and SAIN domains, between amino acids 108 and 516 of IRS-1 that are sufficient for receptor interaction. However, their precise function in mediating insulin's bioeffects is not understood. We expressed the PTB and SAIN domains of IRS-1 in HIRcB fibroblasts and 3T3-L1 adipocytes utilizing replication-defective adenoviral infection to investigate their role in insulin signalling. In both cell types, overexpression of either the PTB or the SAIN protein caused a significant decrease in insulin-induced tyrosine phosphorylation of IRS-1 and Shc proteins, IRS-1-associated phosphatidylinositol 3-kinase (PI 3-K) enzymatic activity, p70s6k activation, and p44 and p42 mitogen-activated protein kinase (MAPK) phosphorylation. However, epidermal growth factor-induced Shc and MAPK phosphorylation was unaffected by the overexpressed proteins. These findings were associated with a complete inhibition of insulin-stimulated cell cycle progression. In 3T3-L1 adipocytes, PTB or SAIN expression extinguished IRS-1 phosphorylation with a corresponding 90% decrease in IRS-1-associated PI 3-K activity. p70s6k is a downstream target of PI 3-K, and insulin-stimulated p70s6k was inhibited by PTB or SAIN expression. Interestingly, overexpression of either PTB or SAIN protein did not affect insulin-induced AKT activation or insulin-stimulated 2-deoxyglucose transport, even though both of these bioeffects are inhibited by wortmannin. Thus, interference with the IRS-1-IR interaction inhibits insulin-stimulated IRS-1 and Shc phosphorylation, PI 3-K enzymatic activity, p70s6k activation, MAPK phosphorylation and cell cycle progression. In 3T3-L1 adipocytes, interference with the IR-IRS-1 interaction did not cause inhibition of insulin-stimulated AKT activation or glucose transport. These results indicate a bifurcation or subcompartmentalization of the insulin signalling pathway whereby some targets of PI 3-K (i.e., p70s6k) are dependent on IRS-1-associated PI 3-K and other targets (i.e., AKT and glucose transport) are not. IR-IRS-1 interaction is not essential for insulin's effect on glucose transport, and alternate, or redundant, pathways exist in these cells.

L38 ANSWER 35 OF 49 MEDLINE on STN DUPLICATE 20

ACCESSION NUMBER: 97197813 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9045663

TITLE: Interaction of the phosphotyrosine interaction/phosphotyrosine binding-related domains of Fe65 with wild-type and mutant Alzheimer's beta-amyloid precursor proteins.

AUTHOR: Zambrano N; Buxbaum J D; Minopoli G; Fiore F; De Candia P; De Renzis S; Faraonio R; Sabo S; Cheetham J; Sudol M; Russo T

CORPORATE SOURCE: Dipartimento di Biochimica e Biotecnologie Mediche, Universita degli Studi di Napoli Federico II, CEINGE Biotecnologie Avanzate s.c. r.l., via S. Pansini 5, 80131 Naples, Italy.

SOURCE: The Journal of biological chemistry, (1997 Mar 7) Vol. 272, No. 10, pp. 6399-405.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 24 Apr 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 14 Apr 1997

AB The two tandem phosphotyrosine interaction/phosphotyrosine binding (PID/PTB) domains of the Fe65 protein interact with the intracellular region of the Alzheimer's beta-amyloid precursor protein (APP). This interaction, previously demonstrated in vitro and in the yeast two hybrid system, also takes place in vivo in mammalian cells, as demonstrated here by anti-Fe65 co-immunoprecipitation experiments. This interaction differs from that occurring between other PID/PTB domain-containing proteins, such as Shc and insulin receptor substrate 1, and activated growth factor receptors as follows: (i) the Fe65-APP interaction is phosphorylation-independent; (ii) the region of the APP intracellular domain involved in the binding is larger than that of the growth factor receptor necessary for the formation of the complex with Shc; and (iii) despite a significant similarity the carboxyl-terminal regions of PID/PTB of Fe65 and of Shc are not functionally interchangeable in terms of binding cognate ligands. A role for Fe65 in the pathogenesis of familial Alzheimer's disease is suggested by the finding that mutant APP, responsible for some cases of familial Alzheimer's disease, shows an altered in vivo interaction with Fe65.

L38 ANSWER 36 OF 49 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 1998158317 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9498552
TITLE: PSM, an insulin-dependent, pro-rich, PH, SH2 domain containing partner of the insulin receptor.
AUTHOR: Riedel H; Wang J; Hansen H; Yousaf N
CORPORATE SOURCE: Department of Biological Sciences, Karmanos Cancer Institute, Wayne State University, Detroit, MI 48202, USA.. hriedel@sun.science.wayne.edu
CONTRACT NUMBER: DK36836 (NIDDK)
SOURCE: Journal of biochemistry, (1997 Dec) Vol. 122, No. 6, pp. 1105-13.
Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF020526
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 22 Apr 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 14 Apr 1998

AB Insulin stimulation results in a considerable spectrum of cellular responses, only part of which have been firmly correlated with the activation of established insulin receptor (IR) targets such as IRS-1, IRS-2, and Shc. Many responses may be transduced by alternative direct IR targets, some of which may still be unknown, may act in parallel to but independently of IRS-1, IRS-2, and Shc, and may be members of the growing family of SH2 domain-containing signaling adaptors. An SH2 domain-coding region of a protein termed PSM was cloned based on its interaction with an activated IR cytoplasmic fragment in a yeast two-hybrid screen. When used as a hybridization probe this region led to the isolation of a protein-coding cDNA which is expressed with a wide tissue distribution and exists in several variant forms. A pleckstrin homology domain and three Pro-rich regions including a putative SH3 domain binding site were identified in addition to the SH2 domain in the deduced 756

amino acid sequence. They imply a role of PSM in tyrosine kinase and phosphatase-mediated signaling pathways. A similar sequence termed SH2-B had been reported in an earlier study, which may represent the rat homolog of PSM. A role of PSM specifically in insulin action is suggested by the interaction of its SH2 domain with an activated but not with an inactive catalytic fragment of the IR in the yeast two-hybrid system in vivo, by the insulin-dependent association of a glutathione S-transferase (GST) PSM SH2 domain fusion protein with purified IR in vitro, and by the insulin-dependent association of GST PSM SH2 with the IR in cell extracts. In contrast, PSM was not found to associate with the established IR substrate IRS-1 under any conditions and appears to act independently of IRS-1. All of our findings are compatible with a putative role of PSM in insulin action.

L38 ANSWER 37 OF 49 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 97352454 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9208849
TITLE: Regulation of the oncogenic activity of BCR-ABL by a tightly bound substrate protein RIN1.
AUTHOR: Afar D E; Han L; McLaughlin J; Wong S; Dhaka A; Parmar K; Rosenberg N; Witte O N; Colicelli J
CORPORATE SOURCE: Department of Microbiology and Molecular Genetics, University of California, Los Angeles, 90095, USA.
CONTRACT NUMBER: CA24220 (NCI)
CA56301 (NCI)
R35CA53867 (NCI)
SOURCE: Immunity, (1997 Jun) Vol. 6, No. 6, pp. 773-82.
Journal code: 9432918. ISSN: 1074-7613.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 12 Aug 1997
Last Updated on STN: 12 Aug 1997
Entered Medline: 28 Jul 1997

AB RIN1 was originally identified by its ability to physically bind to and interfere with activated Ras in yeast. Paradoxically, RIN1 potentiates the oncogenic activity of the BCR-ABL tyrosine kinase in hematopoietic cells and dramatically accelerates BCR-ABL-induced leukemias in mice. RIN1 rescues BCR-ABL mutants for transformation in a manner distinguishable from the cell cycle regulators c-Myc and cyclin D1 and the Ras connector Shc. These biological effects require tyrosine phosphorylation of RIN1 and binding of RIN1 to the Abl-SH2 and SH3 domains. RIN1 is tyrosine phosphorylated and is associated with BCR-ABL in human and murine leukemic cells. RIN1 exemplifies a new class of effector molecules dependent on the concerted action of the SH3, SH2, and catalytic domains of a cytoplasmic tyrosine kinase.

L38 ANSWER 38 OF 49 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 97377002 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9233773
TITLE: Cloning and characterization of APS, an adaptor molecule containing PH and SH2 domains that is tyrosine phosphorylated upon B-cell receptor stimulation.
AUTHOR: Yokouchi M; Suzuki R; Masuhara M; Komiya S; Inoue A; Yoshimura A
CORPORATE SOURCE: Institute of Life Science and Department of Orthopaedic Surgery, Faculty of Medicine, Kurume University, Aikawamachi, Japan.
SOURCE: Oncogene, (1997 Jul 3) Vol. 15, No. 1, pp. 7-15.

Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB000520
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 2 Sep 1997
Last Updated on STN: 2 Sep 1997
Entered Medline: 19 Aug 1997

AB Stimulation of B lymphocytes through their antigen receptor (BCR) results in rapid increases in tyrosine phosphorylation of a number of proteins, which leads to a cascade of biochemical changes that initiates B cell proliferation and differentiation or growth inhibition. A novel cDNA, designed APS, encoding an adaptor protein with a Pleckstrin homology (PH) domain, Src homology 2 (SH2) domain, and a tyrosine phosphorylation site was cloned from a B cell cDNA library using a yeast two hybrid system. APS is structurally similar to SH2-B, an SH2 protein that potentially binds to the immunoreceptor tyrosine-based activation motif (ITAM) as well as Lnk which is postulated to be a signal transducer that links T-cell receptor to phospholipase Cgamma, Grb2 and phosphatidylinositol 3-kinase. APS expressed only in human Burkitt's lymphoma cells among cell lines we examined and tyrosine phosphorylated in response to BCR stimulation. APS bound to Shc irrespective of stimulation and bound to Grb2 after stimulation, suggesting that it plays a role in linkage from BCR to Shc/Grb2 pathway. These results indicate that APS, SH2-B and Lnk form a new adaptor family that links immune receptors to signaling pathways involved in tyrosine-phosphorylation.

L38 ANSWER 39 OF 49 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 97067185 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8910587
TITLE: The inositol 5'-phosphatase SHIP binds to immunoreceptor signaling motifs and responds to high affinity IgE receptor aggregation.
AUTHOR: Osborne M A; Zenner G; Lubinus M; Zhang X; Songyang Z; Cantley L C; Majerus P; Burn P; Kochan J P
CORPORATE SOURCE: Department of Metabolic Diseases, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110, USA.. Jarema.Kochan@roche.com
CONTRACT NUMBER: HL07088 (NHLBI)
HL14147 (NHLBI)
HL16634 (NHLBI)
SOURCE: The Journal of biological chemistry, (1996 Nov 15) Vol. 271, No. 46, pp. 29271-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 7 Jan 1997

AB Immunoreceptors such as the high affinity IgE receptor, FcepsilonRI, and T-cell receptor-associated proteins share a common motif, the immunoreceptor tyrosine-based activation motif (ITAM). We used the yeast tribrid system to identify downstream effectors of the phosphorylated FcepsilonRI ITAM-containing subunits beta and gamma. One novel cDNA was isolated that encodes a protein that is phosphorylated on tyrosine, contains a Src-homology 2 (SH2) domain, inositolpolyphosphate 5-phosphatase activity, three NXXY motifs, several

proline-rich regions, and is called SHIP. Mutation of the conserved tyrosine or leucine residues within the FcepsilonRI beta or gamma ITAMs eliminates SHIP binding and indicates that the SHIP-ITAM interaction is specific. SHIP also binds to ITAMs from the CD3 complex and T cell receptor zeta chain in vitro. SHIP protein possesses both phosphatidylinositol-3,4,5-trisphosphate 5'-phosphatase and inositol-1,3,4,5-tetrakisphosphate 5'-phosphatase activity. Phosphorylation of SHIP by a protein-tyrosine kinase, Lck, results in a reduction in enzyme activity. FcepsilonRI activation induces the association of several tyrosine phosphoproteins with SHIP. SHIP is constitutively tyrosine-phosphorylated and associated with Shc and Grb2. These data suggest that SHIP may serve as a multifunctional linker protein in receptor activation.

L38 ANSWER 40 OF 49 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:367072 SCISEARCH
THE GENUINE ARTICLE: UL250
TITLE: Interaction of insulin receptor substrate-2 (IRS-2) with the insulin and insulin-like growth factor I receptors - Evidence for two distinct phosphotyrosine-dependent interaction domains within IRS-2
AUTHOR: He W M (Reprint); Craparo A; Zhu Y Y; ONeill T J; Wang L M; Pierce J H; Gustafson T A
CORPORATE SOURCE: UNIV MARYLAND, SCH MED, DEPT PHYSIOL, BALTIMORE, MD 21201; UNIV MARYLAND, SCH MED, PROGRAM MOLEC & CELLULAR BIOL, BALTIMORE, MD 21201; NCI, CELLULAR & MOLEC BIOL LAB, NIH, BETHESDA, MD 20892
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (17 MAY 1996) Vol. 271, No. 20, pp. 11641-11645.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 45
ENTRY DATE: Entered STN: 1996
Last Updated on STN: 1996

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Insulin receptor substrate 2 (IRS-2) has recently been shown to be a substrate of the insulin receptor (IR), In this study we utilize the yeast two-hybrid system and assays of in vitro interaction to demonstrate that IRS-2 interacts directly with the IR and the insulin-like growth factor I receptor, We show that, like IRS-1, the region of IRS-2 that contains the putative phosphotyrosine binding and SAIN elements (188-591) is sufficient for receptor interaction and that this interaction is dependent upon the NPX(p)Y (where (p)Y is phosphotyrosine) motifs within the juxtamembrane domains of the receptors, In addition to this amino-terminal NPX(p)Y-binding domain, an additional domain of strong interaction was identified in the central region of IRS-2 and was localized between amino acids 591 and 733, This interaction was found to be dependent upon receptor phosphorylation but was NPX(p)Y-independent, This region does not appear to have either an SH2 or a phosphotyrosine binding domain, Both of the interactions could also be demonstrated in vitro using IRS-2 glutathione S-transferase fusion proteins, We conclude that IRS-2, unlike IRS-1, can interact with tyrosine phosphorylated receptors such as the IR and insulin-like growth factor I receptor via multiple independent binding motifs, Our findings suggest the existence of a previously unidentified phosphotyrosine dependent binding domain within the central region of IRS-2.

L38 ANSWER 41 OF 49 MEDLINE on STN DUPLICATE 25

ACCESSION NUMBER: 96206042 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8654924
TITLE: p150Ship, a signal transduction molecule with inositol polyphosphate-5-phosphatase activity.
AUTHOR: Lioubin M N; Algate P A; Tsai S; Carlberg K; Aebersold A; Rohrschneider L R
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, Seattle, Washington 98104, USA.
CONTRACT NUMBER: CA20551 (NCI)
CA40987 (NCI)
SOURCE: Genes & development, (1996 May 1) Vol. 10, No. 9, pp. 1084-95.
Journal code: 8711660. ISSN: 0890-9369. .
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L36818; GENBANK-P32019; GENBANK-Q01968; GENBANK-U51742
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 8 Aug 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 26 Jul 1996

AB The production, survival, and function of monocytes and macrophages is regulated by the macrophage colony-stimulating factor (M-CSF or CSF-1) through its tyrosine kinase receptor Fms. Binding of M-CSF to Fms induces the tyrosine phosphorylation and association of a 150-kD protein with the phosphotyrosine-binding (PTB) domain of Shc. We have cloned p150 using a modified yeast two-hybrid screen. p150 contains one SH2 domain, two potential PTB-binding sites, an ATP/GTP-binding domain, several potential SH3-binding sites, and a domain with homology to inositol polyphosphate-5-phosphatases. p150 antibodies detect this protein in FDC-P1 myeloid cells, but the same protein is not detectable in fibroblasts. The antibodies immunoprecipitate a 150-kD protein from quiescent or M-CSF-stimulated FDC-P1 cells that hydrolyzes PtdIns(3,4,5)P3, to PtdIns(3,4)P2. This activity is observed in Shc immunoprecipitates only after M-CSF stimulation. Retroviral expression of p150 in FD-Fms cells results in strong inhibition of cell growth in M-CSF and a lesser inhibition in IL-3. Ectopic expression of p150 in fibroblasts does not inhibit growth. This novel protein, p150(ship) (SH2-containing inositol phosphatase), identifies a component of a new growth factor-receptor signaling pathway in hematopoietic cells.

L38 ANSWER 42 OF 49 LIFESCI COPYRIGHT 2007 CSA on STN
ACCESSION NUMBER: 96:95173 LIFESCI
TITLE: Inositols do it all
AUTHOR: Majerus, P.W.
CORPORATE SOURCE: Washington Univ. Sch. Med., Div. Hematol., St. Louis, MO 63110, USA
SOURCE: GENES DEV., (1996) vol. 10, no. 9, pp. 1051-1053.
ISSN: 0890-9369.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: G
LANGUAGE: English

AB Inositol polyphosphate 5-phosphatases (IP5Pases) are Mg super(2+)-dependent enzymes of the phosphatidylinositol signaling pathway. They were initially identified by their ability to hydrolyze inositol 1,4,5-trisphosphate [Ins(1,4,5)P sub(3)] to inositol 1,4-bisphosphate.

Because the substrate mobilizes intracellular calcium ions through the Ins(1,4,5)P sub(3) receptor and the product is inactive in this respect, it was presumed that this enzyme was a signal-terminating enzyme analogous to cyclic nucleotide phosphodiesterase in the cAMP system. However, multiple genes encoding IP5Pases have been discovered in the last few years indicating a much broader role in cell signaling for this family of enzymes. The most recently discovered IP5Pases are a unique group of enzymes that form complexes with other signaling molecules in response to hematopoietic cytokines and growth factors. These newly discovered enzymes provide the first linkage of IP5Pases to tyrosine kinase cell signaling. In this case, binding of macrophage colony-stimulating factor (M-CSF) to its receptor Fms leads to formation of a complex between the receptor, Fms, and adaptor proteins Grb2 and Shc plus a tyrosine-phosphorylated protein of 150 kD designated p150 super(Ship) (SH2-containing inositol phosphatase). p150 super(Ship) encodes a protein that contains two conserved motifs that define IP5Pases. These are GDXN(Y/F)R and P(S/A)W(C/T)DRIL. These conserved residues appear to function directly in catalysis as substitution of any of them with alanine destroys enzyme activity. p150 super(Ship) also contains other motifs characteristic of intracellular signaling molecules, including an SH2 domain, two protein tyrosine-binding (PTB) sites, and several proline-rich regions that bind to SH3 domains. p150 super(Ship) was isolated in a yeast two-hybrid screen based on its ability to be phosphorylated on tyrosine at its PTB-binding site and thereby bind to a bait that contained the PTB domain of Shc. Expression of p150 super(Ship) in FD-Fms cells inhibits growth in response to both M-CSF and IL-3 suggesting that p150 super(Ship) negatively regulates growth in this system. p150 super(Ship) is an IP5Pase, as Kavanaugh et al. and Damen and co-workers have isolated the same protein as one that forms complexes with Grb2 in response to activation by platelet-derived growth factor (PDGF) or by multiple hematopoietic cytokine receptors. This protein was shown to have IP5Pase activity with a unique substrate specificity in that it only hydrolyzed IP5Pase substrates containing phosphate in the 3 position of the inositol ring, that is, Ins (1,3,4,5)-tetrakis phosphate [Ins(1/3,4,5)P sub(4)] and the lipid substrate PtdIns(3,4,5)P sub(3).

L38 ANSWER 43 OF 49 MEDLINE on STN DUPLICATE 26
ACCESSION NUMBER: 96372970 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8776723
TITLE: Evidence for the direct interaction of the insulin-like growth factor I receptor with IRS-1, Shc, and Grb10.
AUTHOR: Dey B R; Frick K; Lopaczynski W; Nissley S P; Furlanetto R W
CORPORATE SOURCE: Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
SOURCE: Molecular endocrinology (Baltimore, Md.), (1996 Jun) Vol. 10, No. 6, pp. 631-41.
Journal code: 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 30 Dec 1996

AB We have used the yeast two-hybrid system to study the interaction between the IGF-I receptor and two putative substrates, IRS-1 and Shc. In addition, we have identified Grb10 as a protein that binds to the insulin-like growth factor I (IGF-I) receptor. This two-hybrid system (the interaction trap) utilizes a hybrid protein

containing the LexA DNA-binding domain fused to the intracellular portion of the IGF-I receptor (LexA-IGFIR beta) and hybrids containing an activation domain fused to either IRS-1 (Ad-IRS-1), Shc (Ad-Shc), or a cDNA library. A positive interaction of LexA-IGFIR beta with the activation domain hybrid results in activation of reporter genes, LacZ and LEU2, in the yeast. Western blotting of extracts from transformed yeast demonstrated that the LexA-IGFIR beta fusion protein was expressed and phosphorylated on tyrosine residues. Coexpression of LexA-IGFIR beta with Ad-IRS-1 resulted in strong activation of both reporter genes; activation did not occur with a kinase-negative receptor mutant. IRS-1 residues 160-516 were sufficient for this strong interaction. Coexpression of LexA-IGFIR beta with Ad-Shc also resulted in strong activation of both LacZ and LEU2 reporter genes. This interaction was also dependent upon a tyrosine kinase-active receptor and required tyrosine 950 in the juxtamembrane region of the receptor. An N-terminal fragment of Shc (amino acids 1-232) interacted almost as strongly as full-length Shc whereas the Shc SH2 domain only activated the more sensitive LEU2 reporter. Full-length Shc was phosphorylated on tyrosine when coexpressed with IGFIR beta but not when coexpressed with the kinase-negative receptor mutant. To identify additional proteins that interact with the IGFIRs, a human fetal brain cDNA library was screened using the interaction trap system. This analysis identified partial cDNAs for Grb10. Coexpression of LexA-IGFIR beta with Ad-Grb10 resulted in strong activation of both LacZ and LEU2 reporter genes; this interaction was dependent upon a tyrosine kinase-active receptor but did not require tyrosine 950.

L38 ANSWER 44 OF 49 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1996:860802 SCISEARCH
THE GENUINE ARTICLE: VV171
TITLE: The intracellular cytoplasmic domain of the Alzheimer's disease amyloid precursor protein interacts with phosphotyrosine-binding domain proteins in the yeast two-hybrid system
AUTHOR: McLoughlin D M (Reprint); Miller C C J
CORPORATE SOURCE: INST PSYCHIAT, DEPT NEUROSCI, LONDON SE5 8AF, ENGLAND; INST PSYCHIAT, DEPT NEUROSCI, LONDON SE5 8AF, ENGLAND; INST PSYCHIAT, DEPT PSYCHOL, LONDON SE5 8AF, ENGLAND; INST PSYCHIAT, DEPT OLD AGE PSYCHIAT, LONDON SE5 8AF, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: FEBS LETTERS, (18 NOV 1996) Vol. 397, No. 2-3, pp. 197-200

ISSN: 0014-5793.
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 27
ENTRY DATE: Entered STN: 1996
Last Updated on STN: 1996
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have used the yeast two-hybrid system to screen for proteins that interact with the carboxy-terminal domain of APP, Six different clones mere isolated and sequence analyses revealed that they encoded domains of a previously described neuronal protein Fe65, a homologue of Fe65 and a homologue of protein X11, All of these proteins contain one or more phosphotyrosine binding (PTB) domains, PTB domain proteins bind to the sequence Asn-Pro-X-Tyr when the Tyr is phosphorylated and are believed to function in signal transduction, APP contains such a motif, These results are consistent with a role for APP in signal transduction mechanisms.

L38 ANSWER 45 OF 49 MEDLINE on STN DUPLICATE 27
ACCESSION NUMBER: 96125056 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8537337
TITLE: The regions of the Fe65 protein homologous to the phosphotyrosine interaction/phosphotyrosine binding domain of Shc bind the intracellular domain of the Alzheimer's amyloid precursor protein.
AUTHOR: Fiore F; Zambrano N; Minopoli G; Donini V; Duilio A; Russo T
CORPORATE SOURCE: Dipartimento di Biochimica e Biotecnologie Mediche, Universita degli Studi di Napoli Federico II, Napoli, Italy.
SOURCE: The Journal of biological chemistry, (1995 Dec 29) Vol. 270, No. 52, pp. 30853-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X60469
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 21 Feb 1996
Last Updated on STN: 6 Feb 1998
Entered Medline: 8 Feb 1996

AB Fe65 is a protein mainly expressed in several districts of the mammalian nervous system. The search of protein sequence data banks revealed that Fe65 contains two phosphotyrosine interaction (PID) or phosphotyrosine binding (PTB) domains, previously identified in the Shc adaptor molecule. The two putative PID/PTB domains of Fe65 were used to construct glutathione S-transferase-Fe65 fusion proteins. Co-precipitation experiments demonstrated that the Fe65 PID/PTB domains interacted with several proteins of apparent molecular mass 135, 115, 105, and 51 kDa. The region of Fe65 containing the PID/PTB domains was used as a bait to screen a human brain cDNA library in yeast by the two-hybrid system. Three different cDNA clones were isolated, two of which contain overlapping segments of the cDNA encoding the COOH terminus of the Alzheimer's beta-amyloid-precursor protein (APP), that represents the short intracellular domain of this membrane protein. The third clone contains a cDNA fragment coding for the COOH terminus of the human counterpart of a mouse beta-amyloid-like precursor protein. The alignment of the three APP encoding cDNA fragments found in the screening suggests that the region of APP involved in the binding is centered on the NPTY sequence, which is analogous to that present in the intracellular domains of the growth factor receptors interacting with the PID/PTB domain of Shc.

L38 ANSWER 46 OF 49 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:686366 SCISEARCH
THE GENUINE ARTICLE: RY909
TITLE: DISTINCT MODES OF INTERACTION OF SHC AND INSULIN-RECEPTOR SUBSTRATE-1 WITH THE INSULIN-RECEPTOR NPEY REGION VIA NON-SH2 DOMAINS
AUTHOR: HE W M (Reprint); ONEILL T J; GUSTAFSON T A
CORPORATE SOURCE: UNIV MARYLAND, SCH MED, DEPT PHYSIOL, BALTIMORE, MD 21201; UNIV MARYLAND, SCH MED, PROGRAM MOLEC & CELLULAR BIOL, BALTIMORE, MD 21201
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (6 OCT 1995) Vol. 270, No. 40, pp. 23258-23262.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650

ROCKVILLE PIKE, BETHESDA, MD 20814.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 44
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Insulin receptor substrate 1 (IRS-1) and src homology and collagen protein (SHC) are signaling proteins which are rapidly phosphorylated on tyrosines after insulin receptor (IR) activation. We have recently shown that both SHC and IRS-1 interact with the tyrosine-phosphorylated NPEY motif of the PR and insulin-like growth factor I receptor via non-SH2 domains (Gustafson, T. A., He, W., Craparo, A., Schaub, C. D., and O'Neill, T. J. (1995) Mel. Cell. Biol. 15, 2500-2508; O'Neill, T. J., Craparo, A., and Gustafson, T. A. (1994) Mel. Cell. Biol. 14, 6433-6442; Craparo, A., O'Neill, T. J., and Gustafson, T. A. (1995) J. Biol. Chemical 270, 15639-15643). In this study we characterize these interactions by examining the effects of 18 amino acid substitutions within and around the IR NPEY motif upon interaction with SHC and IRS 1. We confirm that Tyr-960 within the NPEY motif of the IR is essential for both IRS-1 and SHC interaction and that Asn 957 and Pro-958 are essential for IRS-1 interaction and important but not critical for SHC interaction. Additional mutations surrounding the NPEY motif revealed completely distinct patterns of interaction for SHC and IRS-1. Specifically, mutation of Leu-952 or Tyr-953 (at positions -7 and -8 from Tyr-960) markedly reduced IRS-1 interaction but had no effect upon SHC interaction. Likewise, mutation of Ala-963 (+3) reduced IRS-1 but not SHC interaction. Conversely, substitution of Leu-961 (+1) with either Ala or Arg reduced SHC interaction by 70 and 90%, respectively, yet had no effect upon interaction with IRS-1. Our data show that the sequences within and surrounding the NPEY contribute differentially to either SHC or IRS-1 recognition. Our findings suggest mechanisms by which the differential interaction of known receptors with IRS-1 and SHC may be mediated.

L38 ANSWER 47 OF 49 MEDLINE on STN DUPLICATE 28
ACCESSION NUMBER: 95318150 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7541045
TITLE: Non-SH2 domains within insulin receptor substrate-1 and SHC mediate their phosphotyrosine-dependent interaction with the NPEY motif of the insulin-like growth factor I receptor.
AUTHOR: Craparo A; O'Neill T J; Gustafson T A
CORPORATE SOURCE: Department of Physiology, University of Maryland School of Medicine, Baltimore 21201, USA.
CONTRACT NUMBER: DK44093 (NIDDK)
GM08181 (NIGMS)
SOURCE: The Journal of biological chemistry, (1995 Jun 30) Vol. 270, No. 26, pp. 15639-43.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 17 Aug 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 1 Aug 1995

AB Insulin receptor substrate-1 (IRS-1) and SHC become rapidly phosphorylated upon tyrosines after insulin-like growth factor I receptor

(IGFIR) activation. In this study we demonstrate that IRS-1, SHC , and the p85 subunit of phosphatidylinositol 3-kinase interact directly and specifically with the IGFIR. The interaction of all three proteins is dependent upon IGFIR kinase activity and, furthermore, substitution of Tyr-950 with Phe within the NPEY motif of the IGFIR eliminated interaction with both SHC and IRS-1 but had no effect upon p85 interaction. We show that residues 160-516 of IRS-1 and 1-238 of SHC are sufficient and necessary for receptor interaction in the yeast two-hybrid assay. We also demonstrate a direct in vitro interaction between the IGFIR and a fusion protein containing SHC amino acids 1-238. No interaction was observed with a SHC protein containing only the SH2 domain. We conclude that SHC and IRS-1 interact with the tyrosine-phosphorylated NPEY motif of the IGFIR, and that both proteins interact via related motifs located in their amino termini. We conclude that the interactions of SHC and IRS-1 with the IGFIR are similar to those which we have previously defined with the insulin receptor.

L38 ANSWER 48 OF 49 MEDLINE on STN DUPLICATE 29
ACCESSION NUMBER: 95257931 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7537849
TITLE: Phosphotyrosine-dependent interaction of SHC and insulin receptor substrate 1 with the NPEY motif of the insulin receptor via a novel non-SH2 domain.
AUTHOR: Gustafson T A; He W; Craparo A; Schaub C D; O'Neill T J
CORPORATE SOURCE: Department of Physiology, University of Maryland School of Medicine, Baltimore 21201, USA.
CONTRACT NUMBER: DK44093 (NIDDK)
GM08181 (NIGMS)
SOURCE: Molecular and cellular biology, (1995 May) Vol. 15, No. 5, pp. 2500-8.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 15 Jun 1995
Last Updated on STN: 3 Mar 2000
Entered Medline: 2 Jun 1995

AB The SHC proteins have been implicated in insulin receptor (IR) signaling. In this study, we used the sensitive two-hybrid assay of protein-protein interaction to demonstrate that SHC interacts directly with the IR. The interaction is mediated by SHC amino acids 1 to 238 and is therefore independent of the Src homology 2 domain. The interaction is dependent upon IR autophosphorylation, since the interaction is eliminated by mutation of the IR ATP-binding site. In addition, mutational analysis of the Asn-Pro-Glu-Tyr (NPEY) motif within the juxtamembrane domain of the IR showed the importance of the Asn, Pro, and Tyr residues to both SHC and IR substrate 1 (IRS-1) binding. We conclude that SHC interacts directly with the IR and that phosphorylation of Tyr-960 within the IR juxtamembrane domain is necessary for efficient interaction. This interaction is highly reminiscent of that of IRS-1 with the IR, and we show that the SHC IR-binding domain can substitute for that of IRS-1 in yeast and COS cells. We identify a homologous region within the IR-binding domains of SHC and IRS-1, which we term the SAIN (SHC and IRS-1 NPXY-binding) domain, which may explain the basis of these interactions. The SAIN domain appears to represent a novel motif which is able to interact with autophosphorylated receptors such as the IR.

L38 ANSWER 49 OF 49 MEDLINE on STN DUPLICATE 30
ACCESSION NUMBER: 94114591 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8286433
TITLE: The role of p21ras in receptor tyrosine kinase signaling.
AUTHOR: Medema R H; Bos J L
CORPORATE SOURCE: Laboratory for Physiological Chemistry, Utrecht University, The Netherlands.
SOURCE: Critical reviews in oncogenesis, (1993) Vol. 4, No. 6, pp. 615-61. Ref: 470
Journal code: 8914610. ISSN: 0893-9675.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 12 Mar 1994
Last Updated on STN: 3 Mar 2000
Entered Medline: 24 Feb 1994

AB The notion that ras proteins are required for the stimulation of mitogenesis by different receptor tyrosine kinases (RTKs) has spurred researchers to investigate the precise role of p21ras in signal transduction. A large number of stimuli can drive p21ras in the active conformation, and several proteins that play an important role in regulating the GTP/GDP balance on p21ras have been identified. Indeed, activation of p21ras has been demonstrated to occur by stimulation of guanine nucleotide-releasing proteins (GNRPs) or inhibition of GTPase-activating proteins (GAPs). Moreover, a number of SH2 -containing proteins have been implicated in this signaling pathway, such as shc and sem-5/grb2. On the other hand, downstream signaling from p21ras involves an important protein kinase cascade. This pathway seems to be conserved in evolution, and analogous routes have been described in organisms such as yeast, nematodes, and fruit flies. Nevertheless, the direct effector molecule of p21ras that could couple to this kinase cascade is still unknown. Some indications have been obtained that suggest that this function might be partially performed by p120GAP. This review gives an overview of the role of p21ras in signaling from diverse RTKs. Elucidation of this pathway will improve our understanding of mitogenic signaling pathways and the basis of cancer.

=> d his

(FILE 'HOME' ENTERED AT 12:15:45 ON 27 JUL 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 12:16:16 ON 27 JUL 2007

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L1        14021 S BONE (W) (REPAIR? OR IMPLANT? OR REPLCA?)
L2         1588 S COLLAGEN AND L1
L3          202 S MINERAL AND L2
L4           67 S COMPOSIT? AND L3
L5           56 DUP REM L4 (11 DUPLICATES REMOVED)
L6            7 S (PORE OR DENSITY OR CM2) AND L5
                E LI S T/AU
L7          701 S E3
                E YUEN D/AU
L8           67 S E3
                E CHEN H C/AU
L9         4244 S E3
L10        5010 S L7 OR L8 OR L9
L11           0 S L3 AND L10
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FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 14:17:25 ON 27 JUL 2007

L12	1090	S	MAPKAP (W)KINASE##
L13	2622	S	"MK2"
L14	0	S	HEP25/27 (W)KINASE?
L15	0	S	HEP25(W)27 (W)KINASE?
L16	0	S	HEP25### (W)KINASE?
L17	3551	S	L12 OR L13
L18	12206	S	"SHC" OR "SRC (W)HOMOLOGY?"
L19	11	S	L17 AND L18
L20	8		DUP REM L19 (3 DUPLICATES REMOVED)
L21	36782	S	"SH2" OR "PTB" OR "COLLAGEN HOMOLOGY DOMAIN"
L22	5	S	L12 AND L21
L23	5		DUP REM L22 (0 DUPLICATES REMOVED)
L24	1	S	L13 AND L21
L25	5	S	L13 AND L18
L26	492	S	MAP (W)KINASE-ACTIVATED(W) PROTEIN?
L27	3	S	L21 AND L26
		E	YANNONI Y/AU
L28	48	S	E3-E6
		E	LIN L L/AU
L29	521	S	E3
L30	565	S	L28 OR L29
L31	5	S	L18 AND L30
L32	2		DUP REM L31 (3 DUPLICATES REMOVED)
L33	1465	S	L21 AND YEAST?
L34	0	S	L13 AND L33
L35	0	S	L17 AND L33
L36	5973	S	L18 AND (INTERACT OR BIND? OR ATTACH?)
L37	167	S	L33 AND L36
L38	49		DUP REM L37 (118 DUPLICATES REMOVED)

	L #	Hits	Search Text
1	L1	1	MAPKAP adj "kinase2"
2	L2	821	"MK2"
3	L3	3626	"shc" or (SRc adj homology)
4	L4	1	l2 same l3
5	L5	7153	MAP adj kinase
6	L6	290	l3 same l5
7	L7	118462	yeast$2
8	L8	16	l6 same l7
9	L9	115061	YANNONI LIN
10	L10	12	l8 and l9

	Document ID	Kind Codes	Source	Issue Date	Pages	Title
1	US 20070031823 A1		US-PGPUB	20070208	625	BIOINFORMATICALLY DETECTABLE GROUP OF NOVEL VACCINIA REGULATORY GENES AND USES THEREOF
2	US 20060275900 A1		US-PGPUB	20061207	141	Methods for in vitro expansion and transdifferentiation of human pancreatic acinar cells into insulin-producing cells
3	US 20060216730 A1		US-PGPUB	20060928	371	Novel human protein kinases and protein kinase-like enzymes
4	US 20060204994 A1		US-PGPUB	20060914	71	Novel human protein kinases and protein kinase-like enzymes
5	US 20060188974 A1		US-PGPUB	20060824	131	Human protein kinases and protein kinase-like enzymes
6	US 20060140954 A1		US-PGPUB	20060629	142	Novel human protein kinases and protein kinase-like enzymes
7	US 20060068414 A1		US-PGPUB	20060330	144	Identification of aging genes through large-scale analysis
8	US 20050125852 A1		US-PGPUB	20050609	215	Novel kinases
9	US 20040197792 A1		US-PGPUB	20041007	190	Novel Kinases
10	US 20040048310 A1		US-PGPUB	20040311	152	Novel human protein kinases and protein kinase-like enzymes
11	US 20030224378 A1		US-PGPUB	20031204	73	Novel human protein kinases and protein kinase-like enzymes
12	US 20030211989 A1		US-PGPUB	20031113	86	Novel human protein kinases and protein kinase-like enzymes

	Document ID	Kind Codes	Source	Issue Date	Pages	Title
1	US 20070054268 A1		US-PGPUB	20070308	264	Methods of diagnosis and prognosis of ovarian cancer
2	US 20070031823 A1		US-PGPUB	20070208	625	BIOINFORMATICALLY DETECTABLE GROUP OF NOVEL VACCINIA REGULATORY GENES AND USES THEREOF
3	US 20060275900 A1		US-PGPUB	20061207	141	Methods for in vitro expansion and transdifferentiation of human pancreatic acinar cells into insulin-producing cells
4	US 20060216730 A1		US-PGPUB	20060928	371	Novel human protein kinases and protein kinase-like enzymes
5	US 20060204994 A1		US-PGPUB	20060914	71	Novel human protein kinases and protein kinase-like enzymes
6	US 20060188974 A1		US-PGPUB	20060824	131	Human protein kinases and protein kinase-like enzymes
7	US 20060172923 A1		US-PGPUB	20060803	21	Method of activating insulin receptor substrate-2 to stimulate insulin production
8	US 20060140954 A1		US-PGPUB	20060629	142	Novel human protein kinases and protein kinase-like enzymes
9	US 20060068414 A1		US-PGPUB	20060330	144	Identification of aging genes through large-scale analysis
10	US 20050125852 A1		US-PGPUB	20050609	215	Novel kinases
11	US 20040197792 A1		US-PGPUB	20041007	190	Novel Kinases
12	US 20040048310 A1		US-PGPUB	20040311	152	Novel human protein kinases and protein kinase-like enzymes

13	US 20030224378 A1		US-PGPUB	20031204	73	Novel human protein kinases and protein kinase-like enzymes

	Document ID	Kind Codes	Source	Issue Date	Pages	Title
14	US 20030211989 A1		US-PGPUB	20031113	86	Novel human protein kinases and protein kinase-like enzymes
15	US 6077673 A		USPAT	20000620	15	Mouse arrays and kits comprising the same
16	US 5817479 A		USPAT	19981006	30	Human kinase homologs

10/523014

	L #	Hits	Search Text
1	L1	1	"4522811".pn.
2	L2	1	"4554101".pn.
3	L3	6	"4609546".pn. or "4640835".pn. or "4766106".pn. or "4791192".pn. or "5116944".pn. or "5414135".pn. or "5864""."020".pn.
4	L4	12781	kinase adj inhibitor$2
5	L5	7785	map adj kinase$2
6	L6	3031	l4 and l5
7	L7	1975	"shc"
8	L8	186	l6 and l7
9	L9	259	sh2 adj bind$3
10	L10	239	MAPKAP adj2 kinase
11	L11	0	l9 and l10
12	L12	22	l7 and l10
13	L13	1	"6420338".pn.
14	L14	1	inhibitor$2 and l13
15	L15	1	MAPKAP adj2 kinase adj inhibitor$2
16	L16	0	l1 and l4
17	L17	0	l1 and l14
18	L18	1	l14 and inhibitor$2
19	L19	1	l14 and activator$2
20	L20	5661	l4 and activator$2
21	L21	0	l10 adj activator$2
22	L22	3	MAPKAP adj2 kinase adj10 activator$2
23	L23	3	MAPKAP adj2 kinase adj10 agonist$2
24	L24	0	l7 and l23
25	L25	22	l10 and l7
26	L26	1	"MAPKAP-2 kinase"
27	L27	175	"MAPKAP kinase 2"
28	L28	17	l27 and l7
29	L29	428	l7 and "sh3"
30	L30	174	l7 same "sh3"
31	L31	0	l27 and l30

32	L32	0	110 and 130
33	L33	5	"MK@" and 130

	L #	Hits	Search Text
34	L34	0	"MK2" and l30
35	L35	0	l10 and l30

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=> d his

     (FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007
L1         12209 S "SHC"
L2         17027 S SH3 (W)DOMAIN
L3           588 S L1 AND L2
L4          2640 S "MAPKAP2 KINASE?" OR "MK2"
L5             0 S L3 AND L4
L6          2372 S MAPKAP####
L7             1 S L3 AND L6
L8             5 S L1 AND L4
L9             2 DUP REM L8 (3 DUPLICATES REMOVED)
L10        12209 S "SHC#"
L11          312 S KINASE(W) BINDING (W)DOMAIN?
L12            6 S L1 AND L11
L13            1 DUP REM L12 (5 DUPLICATES REMOVED)
L14           13 S L4 AND (PROLINE (W)RICH)
L15            3 DUP REM L14 (10 DUPLICATES REMOVED)
L16            0 S L4 (3W)TRAGET?
L17            0 S L6 (2W)TRAGET?
L18            2 S L6 (2W)TARGET?
L19           44 S L4 (3W)TARGET?
L20            0 S L19 AND L10
L21            9 DUP REM L19 (35 DUPLICATES REMOVED)
L22            0 S L4 AND "66K##"
L23           13 S L10 AND (L6 OR L4)
L24           10 DUP REM L23 (3 DUPLICATES REMOVED)
```

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                  patents
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